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SYMPOSIUM ON ARTHRITIS

THE PRESENT STATUS OF THE PROBLEM OF ARTHRITIS

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THE problem of arthritis has recently entered upon a new phase of development. Stagnant and neglected for many years, interest in it has been revived and has become active. Clinics for the study and treatment of the disease have arisen within the last three or four years in all parts of the country.

It may be well to enumerate briefly at the outset the chief developments which have taken place in regard to the problem of arthritis both internally and externally. They are as follows:

Recognition of the economic importance of arthritis, with consequent pressure from the industrial world that more be done about it; establishment of the American Committee for the Control of Rheumatism for cooperation in an almost world-wide investigation of the question; general recognition of two main morphologic types of the disease; recognition of hereditary and constitutional influences, together with the existence of prodromata which often allow the disease to be anticipated; evaluation of the problem of focal infection, to which extreme values have often been attached; renewed investigations of joint tissus for infecting organisms; appreciation of the existence of a disturbance of physiology, the so-called dynamic pathology, which is at least partly responsible for the actual morphologic changes and symptomatology of the disease; recognition of the rationale back of certain useful forms of therapy; extension of the application of these forms of therapy and the development of new measures along the same lines; fuller evidence leading to appreciation of some of the factors operative to produce and perpetuate the disease, especially through the intestinal tract, together with various therapeutic implications attaching to this; wider recognition of the influence of body posture upon develop-

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ment or correction of the disease syndrome; and, finally, a greatly widened outlook in general, with justifiable optimism for betterment or even cure of at least three-fourths of all patients under properly controlled and dispassionate conditions of therapy.

In the relatively limited opportunity which presents for the survey of this extensive field it will be impossible to do more than touch upon the several headings indicated with the aim of showing their related nature and telling a more or less connected story.

In view of the exposition which will doubtless be made by other contributors to this number, it is unnecessary to enter upon the question of statistics further than to say that in Berlin alone arthritis is a cause of three to four times more disability requiring pension payments, than is tuberculosis. In Massachusetts, arthritis disability involves about 150,000 persons, in contrast to 75,000 cases of tuberculosis. That this protean disease should have been allowed to engraft itself to this degree upon the community for so many generations of a supposedly enlightened era, affords a commentary upon the extent to which our profession sometimes plumes itself upon its perspicacity and breadth of view.

The question of the morphology of arthritis will also be touched upon by others and suffice it to say here that recognition of two main types of the disease, atrophic or hypertrophic, constitutes an advance of real importance. It is again worthy of comment that about twenty years elapsed between publication by Nichols and Richardson of their classic monograph on this subject, probably the best in any language, and recognition of the value of this classification, not to say acceptance of it, by the American medical public. Even this supposedly simple step has been achieved by virtue, chiefly, of the rather isolated efforts of the small band of individuals who have kept this topic alive and insisted upon its great importance.

In my opinion, in agreement with the conclusion reached by Glover of the British Ministry of Health, there are some other types still to be classified. Rigid acceptance of atrophic and hypertrophic arthritis as wholly discrete and independent diseases was not intended by Nichols and Richardson and is hardly justified philosophically or clinically.

In a long series of arthritics studied by Peirce and myself, heredity played a surprisingly large rôle. In conjunction with the splendid anthropomorphic studies of Osgood, Goldthwait and their collaborators, this makes it necessary to recognize that a certain body habitus underlies much of the disease as a whole and the atrophic type in particular.

From the above considerations it must appear that the etiologic factors of the rheumatoid syndrome are varied and not as simple as has seemed to many persons to be the case. The definite but limited achievements of the doctrine of focal infection have resulted in the usual extreme oscillations of the pendulum of medical opinion which follow upon any advance. Whenever one attempts to analyze the nature of the influence of infection it seems to be necessary first to disarm those who feel that an assault is being made upon a sacred tenet. No undermining of sober thought is attempted, however, on the part of those interested in studying the tissue and functional changes productive of arthritic lesions. Focal infection plays a very important precipitating rôle in the ex-

istence of many conditions and perhaps in no other more than in arthritis. Even when it does so act, however, the rôle is one of precipitation rather than, fundamentally, of causation. The world is full of individuals surcharged with focal infections yet wholly free from arthritis. Nor does removal of infections necessarily make the arthritic well or even better. Medical interest has been focusing too long upon the caliber of the bullet which killed the man in the holdup; and too little upon the state of society which encourages and permits holdups to occur at all. It can be made clear today to any dispassionate mind that factors apparently unrelated to bacteriologic activity and infection, in the usual sense of the word, may bring about the symptoms of arthritis of either atrophic or hypertrophic type.

Following recognition of the importance of focal infection, Rosenow, Haden, and others, many years ago, isolated various organisms, chiefly streptococci, from the joints and other tissues. Recently Shands et al., have recovered streptococci, staphylococci, and even the gonococcus from the joints and neighboring tissues. Cecil has described a strain of streptococcus which he regards as causative and Small entertains comparable views toward the indifferent streptococcus, isolated by him from cases of rheumatic fever; and renamed by him, according to Hitchcock,[1] the streptococcus cardioarthritidis.

There can be little doubt that, precisely as arthritics may harbor many foci of infection, so they may sometimes harbor any of several organisms, in the joints or other structures. Actual purulent joints are met with, although very rarely in chronic arthritis. Whether these organisms, however, are there in a causative relationship, or more in the rôle of invaders from without, is not so clear. Certain it is that apparently normal people may harbor massive focal infection. The factor which makes focal infection operative to produce arthritis, is farther to seek; and it is therefore equally clear that consideration must be given to the factors which permit or induce invasion of joint or other tissues by bacteria in arthritis, when indeed, this does actually occur.

The many uncertainties in this vexed field, the division of views, the contradictory results of bacteriologic study and especially the ease of contamination have given rise to the increasingly accepted viewpoint that the bacteriologic influence in arthritis may be referable partly or largely to an allergic basis.

Space forbids development of this complicated problem and some consideration must be given to the changes in the fluid and fixed tissues which accompany, and are at least partly responsible for, the clinical and morphologic phenomena of the disease.

A long series of studies has been carried out by my associates and myself[2] which helps to explain the nature of the disease and forms the basis for certain advanced types of therapy. Without going into details, it may be said by way of summary that the subject of chronic arthritis, of either type, tends to present, in the absence of fever, a slight lowering of basal metabolism. This is not due to any inborn error of metabolism per se, but apparently to curtailment of the circulation to those tissues, especially the muscles, which have to do with processes of oxidation. Another result of this curtailment of blood supply is a delay in the rate of removal of substances circulating in the blood stream. Glucose is an example of such a substance and, for the reason given, brings

about, when fed to patients with arthritis, in large amounts, a "delayed rate of removal"; erroneously called in this connection a "lowered sugar tolerance." Other observations by Peirce and myself which cannot be described in detail, reveal that the peripheral blood count of the patient with arthritis shows a diminution in the number of red cells in the blood first issuing from a stab, because of the constricted or at least empty condition of the capillary bed. This is further borne out by observations with the thermocouple which show beyond any doubt that the patient with arthritis usually maintains at the periphery a lower temperature than does a normal person. The amplitude of variation of his peripheral temperature is furthermore less than is that of the normal man. This is brought out by subjecting the patient with arthritis to conditions of cold, under which his surface temperature falls less and, afterward, returns more slowly toward normal. This relative immobility of the vascular bed, where the cause of this phenomenon is apparently to be found, explains much of the added disability experienced by the patient with arthritis from those changes in his environmental circumstances occasioned by the weather.

Again, direct observation of the capillary bed of the patient with arthritis under the microscope shows that the vessels present an intermittent and often sluggish blood flow and that they are often relatively empty, sometimes nearly invisible, and of a shape differing from the normal. Direct observation of this field under the influence of measures which benefit the arthritis, such as massage, heat, exercise, aspirin, and the like, may bring about a change in the picture of a highly graphic nature.

In view of these more recent findings it can be mentioned that careful studies of the blood gases in arthritis will show that in a certain proportion of cases there is a slightly increased percentage saturation of oxygen which is apparently due to the fact, referred to above, that the circulating blood inadequately reaches some of the tissues normally concerned in removing certain constituents from it. An interesting corollary to these observations is the fact that by cutting off the blood supply to the patellae of dogs, it has been possible to produce definite overgrowth of the patella,[3] resembling closely hypertrophic arthritis, corroborating earlier experiments along the same line by Wollenberg.

The general point of view here developed has been progressively entertained for about eight years by the writer and his associates.[4] Recently some corroboration of its validity has been forthcoming from another quarter, namely, the influence of the operation of sympathectomy upon certain selected arthritics of advanced type. Adson and Rowntree have shown unmistakably that following this procedure the return of blood supply to the involved parts may be accompanied by striking evidence of subjective and objective benefit.

There is in these several considerations obvious explanation of the rationale underlying the influence of many measures long known to be of value in arthritis. Thus, I and my associates have for some years been studying the influence of heat and massage upon the arthritic syndrome. Omitting details, it seems clear that this highly beneficial influence is referable to the increase and betterment of circulation, not only in the parts chiefly concerned but also in a more systemic sense.

There must now be mentioned a line of observations which bears almost equally upon the etiology, pathology, and treatment of arthritis. Many years ago I became aware of, and described the unusual conditions of the intestinal tract which are present in the course of chronic arthritis and often precede it. This condition is especially to be seen in the colon, because it can there be most satisfactorily studied by the x-ray, and consists in elongation, widening, tortuosity, and inertia of that organ.

These observations were secondary to the attempt to elucidate the influence of a reduced food intake, first emphasized by me in 1912.[5] This subject has recently had interesting and stimulating emphasis at the hands of Fletcher who has shown that, pursuant to proper lines of therapy, the bowel may return toward or to a normal condition, coincidentally with clinical betterment of the arthritic patient as a whole. The means to this end have been dietary and Fletcher lays emphasis upon three main facts: curtailment of the carbohydrate intake; a large vitamin content; and adequate ingestion of protein. It is of great interest to note in this connection that McCarrison,[6] Rowlands,[7] and others have produced in animals precisely the intestinal picture encountered in arthritis, by means of avitamin diets coupled with a large intake of carbohydrate. If the carbohydrate be reduced or if the vitamin be adequate, the pathologic picture does not result; nor does it do so if there be an adequate supply of protein. It has been clearly shown that on this basis infection implants itself readily in many tissues.

The wealth of philosophical considerations contained in these several experiments needs no emphasis. It is plain that factors of a nature much more generic than most of the profession have realized are operative in the production of the rheumatoid syndrome. Furthermore it shows that therapy along orthodox lines, regarded until recently as adequate, may be wholly wide of the mark. This undoubtedly accounts for the failure which has resulted on such a widespread scale following what appeared to be the proper removal of apparently causative focal infection.

As occasionally happens, when the way has been pointed out, the laity, sooner than some of the profession, themselves find out where relief can be obtained. They have therefore begun to flock in large numbers to those obliging persons, largely technicians, often enthusiasts, who will give them the treatments they desire. In this particular instance it becomes partly a question of betterment of function of the intestinal tract through colonic irrigation. Although this measure, under proper precautions, has benefit for many persons, it constitutes only a part of the story. That which is removed by irrigation is of course chiefly that which is introduced by mouth. On this point, in part, and upon others having to do with the metabolism under conditions of an undermaintenance diet, hangs the propriety of dietetic therapy. The question is too large to be entered upon here except to emphasize its importance and indicate where fuller references can be found (loc. cit.). Such therapy involves elements of demerit as well as merit unless there be familiarity with the principles of nutrition but the results in properly chosen cases are usually striking.

Another chapter to which scant attention has been given by the profession as a whole is that relating to the extent to which congenital or acquired body

posture paves the way for, or actually brings about, chronic arthritis. Through visceroptosis and the many causes leading up to it, the intestinal tract achieves, in these improperly made persons, the condition referred to above. Adequate appreciation of this influence makes it often possible to prevent the occurrence of arthritis in persons at large; best illustrated in certain members of families in which the affliction of some members has clearly indicated the probable involvement of others. Furthermore, the sequellae of arthritis may be as serious as the disease itself and when they exist they may constitute additional causes of the disease. The splendid lesson taught by the Boston Orthopedists points the way to break this vicious cycle and to institute in its place a constructive program whose results will delight the heart of every honest and conscientious physician.

There is no opportunity here to enter upon the question of treatment as a whole. It must appear, however, from the above considerations that no single measure suffices to cover this extensive field. For the individual who is so constituted as to make arthritis a possible and early episode in his life, infection may be only as the drop of the flag which starts the race, the stage for the spectacle being set. The inevitable corollary to this is, that while such measures as vaccines have their legitimate place in medicine and also in the treatment of arthritis, they can at best, influence only one factor; if indeed, in arthritis, they often do that. Granting them in arthritis even greater success than they are accredited by sound clinicians, they can in no way change the background on which the disease starts or the consequence of its inroads; and, as a rule, they do not alter the disturbance of physiology which brings about the lesions themselves. I am desirous of making it clear that it is not my purpose to extol or depreciate any one of the many sound measures of therapy available, whether removal of infection, physiotherapy, use of drugs or diet, improvement of intestinal function, betterment of body posture, or what not. Each of these has its place in the complicated program necessary in any attack upon the arthritic problem. To consider arthritis, however, as a disease for which any drug, vaccine, operative, or other procedure is the remedy is to fail to see the problem whole. Now that the medical outlook upon this disease is widening and many new data of precise and clinical nature are available, there is no excuse for approaching this syndrome along the lines of single-minded enthusiasm or prejudice. The time is not far distant when treatment of the hosts of patients with arthritis in the United States, under any outlook which does not comprehend the many important factors in the problem, will be tantamount to a form of malpractice. Indeed, it is so now in the minds of dispassionate students of the subject. An illuminating corollary of this is to be seen in the fact that the various persons who from time to time advocate drug A or vaccine B as affording a specific attack on arthritis, gradually, of necessity, extend their armamentarium when their proclamations have achieved a substantial practice. With the increasing failures which adherence to a limited slogan inevitably brings about, they are driven to utilization of all the measures at the hands of the profession. Eventually these persons usually become saner and more rounded out; and, like the homeopaths who have widened their curriculum

to where it approximates that of the regular school, excuse for and practice of their specific tenets ceases.

One therapeutic consequence of large importance follows upon recognition of the two chief types of the disease; namely, that atrophic arthritis tends toward ankylosis and that hypertrophic arthritis does not. Some rest is usually indicated in both varieties but the extent to which it is applied and the accuracy with which the arthritis itself is classified, may determine whether an ankylosed or movable joint is to result. While certain forms of treatment cluster around each variety of arthritis, however, there is no proved justification, clinical or laboratory, for denying patients in either group the benefit from measures of generic value, because of a priori convictions of etiology.

The subject of arthritis is, curiously enough, by way of becoming so popularized that, whereas it was formerly difficult to get adequate attention from the profession for these sufferers, now persons and clinics are turning to this disease in such numbers, with not infrequent immaturity of viewpoint, that it becomes necessary to introduce a restraining hand and advocate dispassion. Arthritis touches more fields of medicine than does any other disease, with the possible exception of syphilis. For this reason its manifold subtleties cannot be learned easily or quickly. In consequence, snap judgments are all too common and the longsuffering laity will continue to suffer until single-minded enthusiasts have shot their bolts and the main body of the profession has caught up. No one is more conscious than I am of the great desirability of more information in this vexed field. By the same token, however, no one is more conscious of the large amount of precise evidence of laboratory and clinical nature bearing on the disease, which already exists. This information is available to anyone who has the interest and pertinacity to seek it. There is perhaps no more important problem before the medical profession today, in terms of persons now living, than that of the desirability of extending this information to the great army of arthritics. It is little short of tragic to realize that countless sufferers from arthritis must approach the grave in wheel chairs merely because available information is not yet sufficiently widely diffused. Under proper conditions of therapy the statistical probabilities of benefit to any given patient with arthritis are definitely in his favor. There are in fact few other chronic diseases for which more can be done.

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RECENT STUDIES OF RHEUMATISM, WITH SPECIAL REFERENCE TO GONORRHEAL ARTHRITIS*

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ONE of the interesting changes in medical teaching during the past decade has grown out of the tendency to unify ideas concerning pathologic states.

In previous years students of medicine learned about peripheral diseases and disregarded the common ground that lay between these varied disturbances: they learned about nephritis, and arthritis, and myocarditis, and gastritis; and disregarded the fact that between many of the diseases which they studied separately, there was a structural connection which itself was primarily responsible for the diseases in the separate peripheral organs.

One of the expressions that recognized this idea early was "cardiovascular-renal disease."

A still later tendency has been to emphasize the vascular tree as the primarily diseased structure and to study the conditions which bring about acute and chronic inflammatory and degenerative processes in the arterial system.

This tendency weakens the idea of specificity to some extent and makes it unnecessary to believe that a certain selective activity is required for the joints to be involved, a certain selective activity for the myocardium, a certain selectivity for the kidneys, and so on. On the other hand it emphasizes the necessity for studying the changes in blood vessels more closely to discover the differences in structural disturbances between a disease like acute rheumatic fever and a disease like hypertensive vascular disease, which has no articular symptoms.

Acute rheumatic fever is one of the diseases in which the involvement of blood vessels has been found throughout the body, affecting organs which yield no symptoms as well as parts that produce the greatest clinical display.

The studies of Swift and of Von Glahn have identified the perivascular lesions in the neighborhood of the joints with those in the heart muscle, the subcutaneous nodule, and the kidney, in this disease. Thus, a disease which students previously regarded as a selective involvement of joints, is found to be not at all a disease of joints but a disease of the vascular tree. So many lesions occur near the joints that the clinical signs of redness, heat, and swelling naturally follow.

The experimental production of arthritis in animals is interesting in illustrating the extra-articular character of the disease and the fact that the disease is also one of blood vessels both in its early and late stages.

In this study, hemolytic streptococci were injected into the ear vein of rabbits. At twenty-four-hour intervals after the injection the animals were

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killed and the tissues of the joints were examined microscopically to discover the place where the lesion about the joint was beginning and how it was developing.

The results showed that the lesion began as a minute hemorrhage definitely outside the joint capsule and that it progressed as it changed into a purulent focus, until several days later, the joint cavity was penetrated and true arthritis established. The second result was that in its later stages the infection showed proliferative vascular changes in all the organs.

Thus one form of bacterial disease affecting joints in rabbits was, in its early stages, an exudative vascular disease and in its late stages a proliferative vascular disease.

Not all forms of bacteria will produce immediate results in the vicinity of joints following intravenous inoculation as will the hemolytic streptococcus and it is likely that in humans a period of time must intervene between the inoculation of bacteria and the production of rheumatism.

During this period of pause, certain changes are taking place in the tissues of the host which have been referred to as allergic.

To the researches of Swift we must look for the arguments which indicate that acute rheumatic fever is a disease which depends for its clinical manifestations on the establishment in the body of a state of allergy. The explanation which Swift gives includes the comparison of acute rheumatic fever with the allergic phenomena of tuberculosis.

This mechanism of allergy is said to be produced in patients by means of an infection by any kind of streptococcus, such as tonsillitis, sinusitis or other local infections.

While the tissues are still in this state of allergy, the further contact of the body with any streptococcus (or its toxin) will precipitate a critical reaction in which the small blood vessels participate, and a typical proliferative lesion (Aschoff body) results. The clinical expression of this reaction is the disease, acute rheumatic fever.

Acute rheumatic fever is therefore not a disease produced by the initial inoculation of streptococci but, according to the Swift hypothesis, is the reaction of an allergized body to further contact with a streptococcus. In other words, if the process of allergy, or the second contact, were avoided the disease might not be produced.

Now in rabbits sodium salicylate will inhibit the development of allergy as expressed by the cutaneous reaction. The clinical usefulness of sodium salicylate in the treatment of acute rheumatic fever may depend on its capacity to suppress, temporarily, the process of allergy. Perhaps x-ray would act in this way, and the beneficial effect of x-ray on rheumatic carditis, reported by Levy, may be thus explained. Neither of these agents, sodium salicylate nor x-ray, can be regarded as antistreptococcal in its action and both are only partially helpful to patients.

The use of vaccines and serums in the treatment of this disease is not yet satisfactorily developed.

This interesting influence of allergy is no doubt at work in many infectious diseases which, until now, have been regarded as simply the reaction

of bodies inoculated with bacteria. Even a disease like lobar pneumonia is probably not produced suddenly in robust subjects, as textbooks frequently state, but more often the explosion follows a week or two during which there has been an allergizing respiratory infection.

It is necessary, therefore, to bear in mind that while the injection of streptococci may be followed immediately by arthritic disease in rabbits, in human beings such an immediate response is by no means easy to observe.

Some intercurrent event is usually necessary to permit the invasion of the blood stream by bacteria which for weeks or years have been retained in a middle ear or a posterior urethra.

Hanger, Swift, and ourselves have shown that animals allergic to one type of bacteria may be killed by the intravenous inoculation of an entirely different and otherwise nonlethal kind of bacteria.

The clinical application of this idea is easily observed in cases of gonorrheal rheumatism. In the first place, the implantation and growth of gonococci in the urethra may or may not lead to a bacteriemia but rheumatism is almost never the immediate accompaniment of urethritis. Nevertheless, the body becomes allergic to gonococci and so remains. The factor responsible for the later production of bacteriemia and rheumatism is an intercurrent infection or intoxication.

During the past few months we have seen an upper respiratory infection exert this influence in three instances; a hemolytic streptococcus infection of the throat once; and food poisoning once.

Gonorrheal rheumatism is a bacterial type of rheumatism. While employing the mechanism of allergy for its production, this form of rheumatism depends for the continuation of its clinical manifestations on the presence of gonococci. It differs from acute rheumatic fever in its persistence and from all other pyogenic forms of rheumatism in its tendency to localize in one or two joints. It occurs in two chief clinical forms: a simple effusion into the joint, or a dense, tender induration of the extra-articular tissues. The place near the joint where the inflammation starts can be detected by the pink area in the skin which overlies the purulent focus. In the effusion types, fluid is easily obtained by puncture. Such fluid contains few gonococci. In the brawny indurations of the other type, fluid is difficult to obtain but in the drop of bloody pus on the needle-tip, gonococci are more easily demonstrated.

In the cases where a large effusion causes the joint to be distended, and where there is no evidence of extra-articular infiltration, the body is usually able to rid itself of the disease and the treatment consists only of tapping and extension of the joint. However, the body is not able to eradicate those extra-articular infiltrations which are rich in gonococci, and while it may receive help from various nonspecific forms of injections, the results are unsatisfactory. The worst treatment is the immobilization of such joints in casts or splints.

The best results are obtained in this group of cases by making an incision through the most congested and tender area to the site of the pus. Evacuation and drainage of this purulent focus has resulted in 20 of our cases, in complete recovery.

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BEAUMONT BUILDING.

THE DIFFERENTIAL DIAGNOSIS OF RHEUMATOID AND OSTEARTHRITIS: THE SEDIMENTATION REACTION AND ITS VALUE*

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I. THE DIFFERENTIAL DIAGNOSIS OF RHEUMATOID AND OSTEARTHRITIS

THE study of chronic multiple arthritis has demonstrated the existence of two separate and distinct disease processes which are conveniently grouped under this general title. The first of these represents a multiple arthritis with additional evidence of a generalized tissue response to an infectious process; the second, a degenerative process involving the joint structures and appearing at a time of life when other degenerative changes are prone to occur. The existence of these two clinical entities is clearly recognized, but the obscurity surrounding their etiology has precluded the adoption of an adequate and generally accepted terminology. The following descriptive terms, employed in the literature devoted to this subject, still meet with greater or less favor.

Synonyms for Group I	Rheumatoid arthritis
	Chronic infectious arthritis
	Atrophic arthritis
	Arthritis deformans (American usage)
	Rheumatic arthritis
	Chronic rheumatic arthritis
	Chronic rheumatism
	Primary progressive polyarthritis
	Secondary progressive polyarthritis

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Synonyms for Group II	Ostearthritis
	Degenerative arthritis
	Hypertrophic arthritis
	Climacteric or menopausal arthritis
	Senile arthritis
	Arthritis deformans (German usage)

The title chosen to designate each particular variety is of small importance so long as it is recognized that the two groups represent distinct clinical and pathologic entities. For the purposes of discussion, however, it is essential that one particular terminology should be at least tentatively adopted.

The terminology most generally employed in America is either one of the following:

I. Chronic infectious arthritis.
II. Degenerative arthritis, or

I. Atrophic arthritis.
II. Hypertrophic arthritis.

The classification adopted by the British Ministry of Health is as follows:

I. Rheumatoid arthritis.
II. Ostearthritis.

The first of the American terminologies, that employed by Cecil,[2] possesses certain definite advantages. It emphasizes the distinction between the infectious and noninfectious forms of arthritis, a differentiation which we feel to be thoroughly justified. Moreover the term *degenerative* suitably describes the type of pathologic process involved in that particular form of the disease.

The British terminology also possesses distinct advantages. The term *rheumatoid* indicates that a relationship exists between this form of chronic arthritis and rheumatic fever, a relationship which we believe to be of great importance. The term *osteo*, while less apt, indicates that this form of arthritis is essentially a disease of the osteoid structures of the joints. In addition, the British classification possesses the advantage of the weight of great authority. Garrod,[1] in 1908, in his classical description of these diseases, adopted the terms rheumatoid and ostearthritis. Since Garrod's time singularly little has been added to our knowledge of these conditions and confusion rather than clearness has resulted from the introduction of new terminologies. In the Arthritic Clinic of the Presbyterian Hospital we have elected to follow the British classification. This classification has been recommended by the International League for the Control of Rheumatism and therefore possesses the advantage of widespread use. The present communication is concerned with the differential diagnosis of these two groups of chronic arthritis.

A third and much less frequent type of chronic arthritis, variously designated as metabolic arthritis, gouty arthritis, or chronic gout is now recognized as a separate disease entity. The differential diagnosis of this form of chronic arthritis only causes difficulty in rare instances. With the aid of the following criteria, as pointed out by Hench,[3] Cecil,[2] and others, the diagnosis can usually be made without danger of error.

1. Classical history of onset with an attack of acute pain in the great toe.

2. The paroxysmal and intermittent nature of the acute and subacute attacks, frequently associated with complete joint remissions.

3. The occurrence of gouty tophi in the ears or about the joints.

4. Increased uric acid content of the blood.

5. Characteristic roentgenologic findings of punched-out areas in the epiphyses of the bones. Such punched-out areas, however, are not infrequently seen in cases of rheumatoid arthritis and this finding should only be considered of value when the areas are quite large and when associated with other manifestations of the disease.

Another sign has frequently been described as characteristic of gout—namely, the occurrence of nodular swellings in the subcutaneous tissue near the joint-structures and along the course of tendon sheaths. Great care, however, must be exercised in differentiating such nodules from similar structures which occur in rheumatoid arthritis.

The two major groups of patients represent entirely different clinical and pathologic states and the first step toward a more intelligent appreciation of

TABLE I

	RHEUMATOID ARTHRITIS	OSTEARTHRITIS
1. Family History	Not infrequently a history of rheumatic fever in an immediate member of family.	Frequently a history of a similar form of arthritis in older members of family.
2. Past History	Occasionally a history of rheumatic fever; frequently a history of tonsillitis or sinusitis.	Not characteristic.
3. Age at Onset	Any age; over 80 per cent between twenty and fifty.	Rare before 40; most frequent 40-55. In women most common at menopause (menopausal arthritis).
4. Mode of Onset	Rarely acute; usually subacute or insidious; often accompanied by migratory pains.	Insidious; not accompanied by migratory pains.
5. Patient's General Condition	Usually undernourished, anemic, and "chronically ill."	Well nourished, frequently obese; not anemic.
6. Evidence of Infection	Frequently slight fever (99°) and slight leucocytosis. Foci of infection usually present.	No fever, no leucocytosis. Foci of infection less common.
7. Joint Involvement	Symmetrical and generalized; proximal interphalangeal joints especially involved.	Usually symmetrical though less generalized; larger joints, particularly knees, but also distal interphalangeal joints involved.
8. Appearance of Joints	Early: Periarticular swelling, fusiform fingers. Late: Ankylosis, extreme deformity, ulnar deflection.	Early: Slight articular enlargement. Late: More pronounced articular enlargement; ankylosis slight and never complete: Heberden's nodes.
9. Muscular Atrophy	Often marked, particularly in later stages.	Not characteristic.
10. Cutaneous Changes	(1) Extremities frequently cold and clammy; skin atrophic and glossy; redness of thenar and hypothenar eminences. (2) Psoriasis occasionally present.	No characteristic features. Not present.
11. Subcutaneous Nodules	Present in 15 to 20 per cent of cases.	Normal or only slightly increased; only rarely above 30 mm.
12. Sedimentation Rate	Usually greatly increased; values above 30 mm. in nearly all active cases.	Early: Slight lipping at joint margins.
13. Roentgenologic Findings	Early: No bony changes, periarticular swelling; slight narrowing of joint spaces. Late: Osteoporosis, bone destruction with new bone formation; ankylosis and deformities.	Late: Marked lipping, osteophyte formation and hyperostosis.

the arthritic problem lies in a more universal recognition of this distinction. For the sake of clearness and conciseness the differential diagnostic points have been arranged in tabular form.

With the aid of these distinguishing characteristics, it has been possible to diagnose the type of arthritis in 95 per cent of the patients who presented themselves for treatment at the Arthritic Clinic of the Presbyterian Hospital. The majority of these differential diagnostic points are well recognized and form the basis for the classification adopted in Great Britain by the Ministry of Health and in America by numerous investigators. In this communication attention is drawn to two particular points in the differential diagnosis of the two groups:

1. The occurrence of subcutaneous nodules near the joint structures and along the course of tendon-sheaths in cases of rheumatoid arthritis. These nodules, varying in size from scarcely palpable, seed-like bodies to excrescences the size of olives, are found in 20 per cent of advanced cases of rheumatoid arthritis. Similar nodules have never been observed in cases of ostearthritis. Histologically these nodules show a striking resemblance to those occurring in rheumatic fever. Preliminary studies on these nodules have been reported by one of us[4] before the American Society of Pathologists and Bacteriologists and more detailed descriptions are in course of preparation.

2. The marked difference in the sedimentation reaction of the erythrocytes in the two conditions. Observations on the sedimentation rate of the red blood cells in rheumatoid and ostearthritis are embodied in the succeeding portion of this paper. By way of further interest the sedimentation rate has been determined in 28 cases of nonarticular rheumatism ("fibrositis," "myositis," "neuritis," etc.).

II. THE SEDIMENTATION RATE OF THE ERYTHROCYTES IN RHEUMATOID AND OSTEARTHRITIS (WITH ADDITIONAL OBSERVATIONS ON 28 CASES OF NONARTICULAR RHEUMATISM)

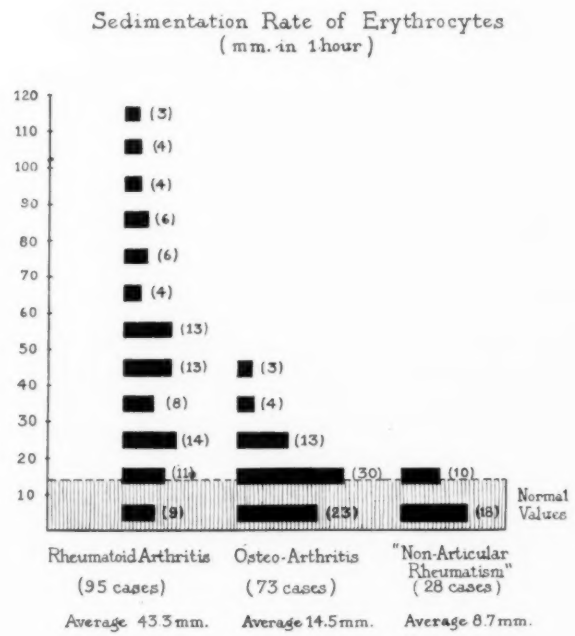
In recent years the determination of the sedimentation rate of the erythrocytes in chronic arthritis has been recognized in European clinics[5] as a procedure of considerable value. In America, however, this test has not received the recognition which it merits. During the past six months at the Arthritic Clinic of the Presbyterian Hospital the determination has been made as a routine procedure on all arthritic patients. Employing Westergren's modification of Fahraeus' original technic, we have made approximately 500 observations on 220 patients who sought treatment in the clinic.

The details of the technic are as follows: Four-tenths c.c. of sterile sodium citrate (3.8 per cent) is drawn up in a 2 c.c. sterile syringe. There is 1.6 c.c. of blood withdrawn from the patient's vein in the same syringe and the mixture transferred to a test tube. A column of the citrated blood 200 mm. in height is drawn up in a 1 c.c. pipette and transferred to a rack, the base of which is formed of plasticine. After one hour the distance which the red blood cells have fallen is measured in mm. This reading is referred to as the Sedimentation Rate. The rate does not vary if the blood is drawn up into the pipette

within two hours of the venepuncture. If a longer period has elapsed there may be a slight decrease in the rate, but no great change occurs until after a period of six hours.

The results of the observations carried out on 196 patients (95 cases of rheumatoid, 73 of osteartbritis, and 28 cases of nonarticular rheumatism) are presented in Table II. These observations were confined solely to patients suffering from chronic multiple arthritis and nonarticular rheumatism ("fibrositis," "myositis," "neuritis," etc.). The values obtained in 24 cases of related conditions, Still's disease, spondylitis, gonococcal arthritis, gout and intermittent hydrarthrosis are considered separately. As a rule several observations were

TABLE II



made on the same patient. In all cases the highest reading obtained has been recorded. Cases with other associated conditions which might affect the sedimentation rate have not been included in this table.

A more careful analysis of the observations made in these three groups of patients reveals the additional information as shown in Table III.

In summary these observations have led to the following conclusions:

1. In active cases of rheumatoid arthritis the sedimentation rate of the red blood cells is, as a rule, greatly elevated, usually attaining values exceeding 30 mm. in one hour.

2. In rheumatoid arthritis the sedimentation rate parallels to an extraordinary degree the severity and extent of the arthritic process.

3. Exacerbations are almost invariably attended by an increase, and remissions by a decrease, in the sedimentation rate.

TABLE III

	NO. CASES	PER CENT
I. *Rheumatoid Arthritis*—		
a. *Values above 30 mm.*	59	62
These cases were distributed as follows:		
"Active" cases	54	56.8
"Arrested" cases	5	5.2
b. *Values below 30 mm.*	36	38.0
These cases were distributed as follows:		
Old, arrested or "cured" cases	25	26.2
Totally cured	2	2.1
Very early cases	2	2.1
Apparently active cases	7	7.3
II. *Ostearthritis*—		
a. *Values above 30 mm.*	9	9.6
b. *Values below 30 mm.*	66	90.4
III. *Nonarticular Rheumatism ("Fibrositis," "Myositis," "Neuritis," etc.)*—		
a. *Values above 30 mm.*	0	0
b. *Values above 12 mm. (normal)*	6	21.4
c. *Values below 12 mm.*	22	78.5
Comparison of Averages:		
a. Rheumatoid arthritis		43.3 mm.
b. Ostearthritis		14.5 mm.
c. Nonarticular rheumatism		8.7 mm.

4. In old, long-continued and arrested cases the sedimentation rate tends to return to normal values.

5. In cases of ostearthritis, on the other hand, the sedimentation rate, while as a rule slightly elevated, rarely attains values greater than 30 mm.

6. All cases of nonarticular rheumatism ("myositis," "fibrositis," "neuritis," etc.) show a normal or only very slightly elevated sedimentation rate.

Additional observations have been made in cases of Still's disease, spondylitis, gout, gonococcal arthritis and intermittent hydrarthrosis.

Still's Disease.—The readings obtained in three cases of Still's disease were as follows: 75, 69, and 22. The first two of these cases were active and progressive; the third had shown definite improvement over a long period.

Spondylitis.—The sedimentation rate was determined in 12 cases of spondylitis. The values obtained varied from 67 to 8 but there was a very distinct difference between the readings in the infectious and noninfectious groups. Those cases that, on clinical grounds, were felt to be the result of an infectious process invariably gave higher readings than those in the osteo (hypertrophic, degenerative) group.

Gonococcal Arthritis.—In seven cases of gonococcal arthritis, values varying between 44 and 9 were obtained. The more acute cases invariably gave the higher readings.

Gout.—In one case of gout during an acute attack, the sedimentation rate was found to be 92. This observation, in conjunction with the findings of others,[7] indicates that this test is of no value in differentiating the arthritis of gout from other types.

Intermittent Hydrarthrosis.—In one case of intermittent hydrarthrosis the determination gave a value of 15.

In conclusion, the distinct clinical value of the determination of the sedimentation rate of the erythrocytes is clearly indicated in the differential diagnosis of rheumatoid and ostearthritis. It must be emphasized, however, that the test should never be relied upon as the sole criterion in the differential diagnosis of the two conditions. This differentiation can usually be made on clinical grounds alone. The determination of the sedimentation time of the red blood cells usually confirms the diagnosis and contributes information of considerable prognostic value in the clinical study of the disease.

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THE SPECIFIC VACCINE TREATMENT OF CHRONIC ARTHRITIS AND RHEUMATISM

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IN THE year 1909, an unmarried woman aged thirty-five whom I had previously known as active, energetic, and healthy, consulted me. She was walking on crutches, and she was suffering from extreme pain in the dorsal and lumbar regions. She told me the following history: some twelve months previously, while abroad, she had consulted a doctor for breathlessness when playing tennis, and general lassitude. The diagnosis made was "tired heart." Rest was ordered. Severe pains in the back then developed. An orthopedic surgeon of note diagnosed tuberculosis of the spine and the patient was kept on her back in a box splint with extension, for six months. The pain grew less but recurred as severely as ever when she began to get up again. Clinically, beyond some muscular spasm there was nothing to be made out. The heart was normal. I came to the conclusion that the condition must be rheumatic. The urine was found to contain numerous streptococci. A vaccine was prepared from these in my laboratory, and after some six weeks of treatment with doses ranging from half a million to two million, the symptoms cleared up completely and have never recurred. This most dramatic case coming as it did after several other more or less successful efforts on the same lines, convinced me once and for all that the vaccine treatment of rheumatic conditions held out the best hope of curing the disease.

Since that time something over two thousand cases have been investigated bacteriologically and treated by autogenous vaccines, with steadily improving results. In 1926 I published an analysis of 490 cases of arthritis and 210 of various forms of nonarticular rheumatism.

Since that time a further 1000 cases show still better results. Not included among these are several hundred cases treated entirely by stock vaccine at the Charterhouse Rheumatism Clinic, Crosby Row, London, S.E.1, where the results are surprisingly good.

When vaccine treatment first came into vogue, it was tried for all possible bacterial diseases, but with the crude early technic many failures occurred, and as a result of a general disappointment the whole method fell rather into disrepute. This was especially the case in rheumatism and chronic arthritis, where the miraculous cures promised failed to materialize. Nor did the more sceptical hesitate to proclaim that as no improvement was to be expected in arthritic cases where bone change had occurred, the bacteriologist had no right to make vaccines and charge his unfortunate dupes the cost of such preparations, knowing full well the utter uselessness of the pro-

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cedure. Even up to the present day the bulk of the medical profession remains quite unconvinced of the value of the method as applied to the chronic rheumatic diseases.

To deal first with the idea that when bony change has occurred no improvement can be expected; this opinion rests on the fallacy that the symptoms are due directly to the bony change, e.g., that the pain is caused by the friction of the denuded bony surfaces. The worst symptoms of chronic arthritis are caused by inflammatory changes in and about the joint, irrespective of the amount of bony change. The pain at night, the tenderness on movement or on pressure, the intolerable aching and burning sensations are all due either to periarticular pressure, or perhaps to the granulomatous cavitation in the bones themselves. The proof of this is twofold: first, that there can be an advanced condition of ostearthritis without any symptoms at all. Second, that notwithstanding the presence of extreme bony change, symptoms may in favorable cases entirely disappear. As an example of the first: a patient complained of pain in the left hip joint, which he had noticed coming on for years. X-ray photographs showed a severe degree of ostearthritis both in the left hip joint and in the right hip joint, and from the radiographs alone it was quite impossible to say which was the worst joint. Yet the patient had never known that he had any trouble at all in his right hip.

Of the fact that the symptoms may disappear despite the severest bone change, I could give endless examples. Here is one published in my book *The Treatment of Chronic Arthritis and Rheumatism* (Oxford Univversity Press, 1926).

"A man, aged fifty-four, suffered for three years with pain in the left hip joint, occasional pain in the left elbow, and inability to sleep owing to the severity of the symptoms. He was considering throwing up his job, that of a farm laborer. Treatment was started in November, 1923. It was carried on steadily until the end of June, 1925. Vaccines consisted of stock streptococci combined with autogenous vaccine prepared from the feces. Here I had found 80 per cent of streptococci of eight different varieties. He never reached very large doses, 30 million was the highest. Toward the end I was giving him only 10 million once a week. He never gave up a day's work throughout the treatment. He soon lost his pain and, except for an occasional bad night, slept well. Apart from a slight limp he now has no symptoms of any kind whatever."

The suggestion then that no improvement can be looked for in cases showing bony change is thus proved to be without foundation. Why, then, has the vaccine treatment of these cases failed so frequently as to render the medical profession entirely sceptical? There are certain very definite and quite sufficient differences in technic (both bacteriologic and clinical) to account for the poor results.

In order to understand the rational basis for the altered technic, a brief review of the successive conceptions of the mechanics of immunization may help. From the days of Pasteur up to the present, innumerable experiments have demonstrated that the effect of the injection of either killed or living but attenuated bacteria is to protect the subject from the disease caused by

that bacterium. The result is the same as that of an attack of the disease itself. Immunity is conferred. This immunity was visualized as something in the blood which killed off any hostile microbes. No doubt the rise in agglutinating, bactericidal, and opsonizing power which is demonstrable in the serum by laboratory methods, tended to crystallize this view. Certainly for many years, immunity was thought to be an affair of antibodies in the blood. The early efforts in vaccine therapy were therefore directed toward raising the blood immunity. Constantly increasing doses were found in many cases to produce a measurable rise in the antibodies. Without entirely ignoring this blood immunity, we now suppose it to be the indicator of a much deeper and more important tissue immunity. For example where a microbe such as B. typhosus attacks a mucous membrane, the cells lining the intestinal wall must be the first and primary barrier, and it is these on which the immunity must have been conferred by the injection. Some confirmation of this view is to be found in the efficient immunity to many intestinal diseases which it is claimed is the result of the oral administration of bili-vaccine.

The earlier purely humeral theory influenced Koch in his treatment with tuberculin. His motto in fact was "the bigger the dose, the better the result." He had some successes, but many failures. Almroth Wright found the clue to some of these, in that he showed that the so-called tuberculin reaction was due to a local flare-up of the disease. The blood supply was increased, the toxic products from bacteria were washed out into the system, causing what he, I think, was the first to name, "autoinoculation." Wright further showed that extra blood supply, undue movement or, in lung disease, increased breathing, had the same effect as an injection of tuberculin, and autoinoculation was produced. This, if sufficiently intense, resulted in an increased area of disease. He then argued that if an injection produced autoinoculation, any successful cases were successful just because of the autoinoculation, and that therefore the right treatment must be to produce artificially, by the injection of a vaccine or otherwise, just such an amount of autoinoculation as would stimulate the system to combat the disease, but not so much as to depress the vitality of the patient so that the disease may progress. Patterson put the idea into practice. By means of carefully graded labor, he cured many tuberculous lungs under regulated autoinoculation. It was but a short step to the view that nature always cured the so-called chronic diseases by this method, and it is certainly a tenable hypothesis that in rheumatism and chronic arthritis, methods of treatment, such as radiant heat, massage, electricity, are beneficial inasmuch as they produce autoinoculation, and detrimental if and where that autoinoculation is too excessive.

In acute diseases the case is different. An invasion occurs of microbes of such virulence that the system immediately revolts. Active inflammatory changes supervene, and all the symptoms of a general and severe illness appear. But in slow and chronic disorders Wright showed by his estimations of the blood immunity that nature is not sufficiently stimulated to bring the forces of attack into play. These must therefore be artificially excited. This he asserted could best be done by the injection of what presumably was a collection of the microbes of the disease more highly concentrated than was

to be found at the site or focus of the disease, in other words, a vaccine. To summarize: formerly a heightened blood immunity was the aim of vaccine treatment. Later this idea has been modified somewhat by the view that controlled autoinoculation was the main object to be kept in view. Neither of these, however, is altogether consistent with more modern views on the irritability of cells in tissues, as exemplified in its most obvious form, namely, allergy. So that we require yet another conception to govern the technic of vaccine treatment. Injections of a vaccine must be so graded in strength and so spaced as to provoke just that amount of response in sensitized tissue cells which will faintly arouse their normal antibacterial powers, but that this action or reaction, if you prefer, is not to be followed by a depression or slowing down of vital processes, when the cells may be more susceptible to bacterial invasion. The real difference is, that we now think in terms of individual cells, and not of the blood immunity, or of certain tissues or organs as a whole. Apart, however, from the clinical treatment side, which means the adjustment of doses and interval, there are certain bacteriologic considerations which here require notice.

From all experiments and observations on vaccine treatment, it is clear that the more specific the vaccine the sharper in definition is the effect.

For successful treatment by vaccines certain conditions must be fulfilled:

1. The actual microbes of the disease must be isolated.

2. They must be capable of culture outside the body. One may perhaps add from personal experience that freshly isolated cultures must be used for the preparation of vaccine if it is to be thoroughly efficient.

It is necessary to examine as to how far these conditions have obtained in the vaccine treatment of rheumatism. What are the microbes of chronic arthritis? There is no doubt, I think, that the majority of research workers and clinicians are convinced that streptococci play a considerable part in the chronic rheumatic diseases. But it is extremely difficult to obtain convincing proof of this supposition. Whatever positive results are obtained, either in investigation or in experiments on animals, there always remains some loophole through which the skeptic can escape from the inevitable conclusion. If streptococi are the cause of arthritis, then in subacute conditions they should be isolated from the blood stream. But they are seldom if ever found. In this connection one might perhaps say that the recent findings of Burbank (Bull. New York Acad. Med. **5**: 176, 1929) have not been confirmed. I myself followed his technic exactly in some 50 consecutive cases, but failed to obtain a single growth of streptococci in any of them. Then again fluid obtained from infected joints is usually sterile. Cultures made from actually affected tissues round and about an arthritic joint, also glands, have occasionally yielded streptococci, but the results on the whole are meager and unconvincing. Nearly all published experiments lack that clear distinction of outline which is so essential to carry conviction. This is largely owing to the general haziness of our knowledge of the streptococcus group, and of our inability to distinguish the members of it, or to assert with sufficient confidence that a certain streptococcus which, for example, we may

have discovered from a lesion produced in a rabbit, is really the same as the streptococcus which we introduced.*

In 1920, the necessity for the differentiation of the streptococci became urgent for clinical reasons; I then introduced the medium now called by my name, and this together with certain standard tests, enables the bacteriologist to assure himself of the identity of any streptococcus with which he may be working, and to recognize it as and when he finds it in connection with disease in man or animals. It has frequently been urged that if autogenous vaccines are being prepared from a given streptococcus, the exact identity of the organism is a matter of but slight importance and certainly not worth an investigation, which before my method was introduced was certainly prolonged and arduous. This view is based on the idea that disease is monobacterial and that the flora underlying is fixed and immutable. My experience negatives that view. In the early days, one frequently found that cases

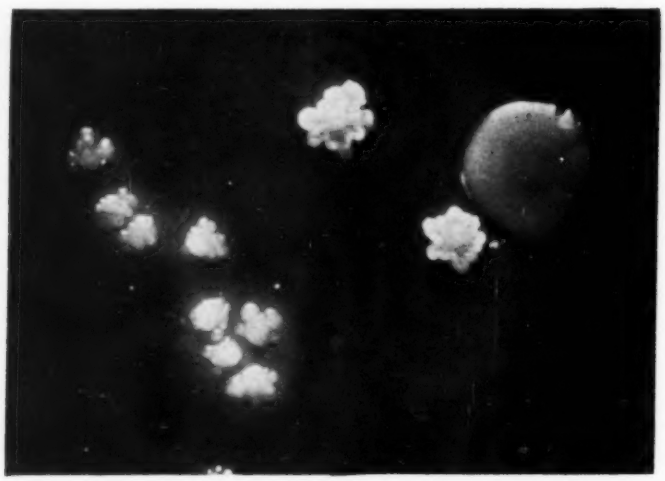

Fig. 1.—Primary culture on Crow's medium from feces in a case of arthritis. Two different varieties of streptococci and a staphylococcus. Magnification by 12.

of arthritis due apparently to intestinal streptococci would improve under autogenous vaccine treatment, but that relapse followed sooner or later. Further examinations then revealed that quite different streptococci were present in the bowel: fresh vaccines were again made and used with temporary benefit. This sequence of events might occur time after time. The same was found in the treatment of chronic bronchitis. An explanation is to be found in the fact that a patient's blood will often agglutinate several different streptococci, some of which may not even be derived from the patient. Full details are given in my book.

In order to render the treatment permanently effective it seemed essential that these various latent streptococci, only a few of which were cultured at a given time, should all be contained in the vaccine. Success was achieved by combining a very polyvalent stock vaccine with the autogenous vaccine

*The evidence in favor of the streptococcal origin of rheumatic diseases is fully set forth in the "Bacteriology and Surgery of Chronic Arthritis and Rheumatism." H. Warren Crowe. Oxford Medical Publications, 1927.

in every case. The preparation of this stock vaccine involved the differentiation and recognition together with classification of every type of streptococcus that could be suspected of being involved in rheumatic cases. By means of photography of colonies on Crowe's medium, and a long series of biologic tests, every streptococcus isolated was cataloged to prevent duplication, and made into a separate vaccine. Eventually these were mixed together in equal amounts. The total number of different organisms was 155. This work has been described in full with all the technic in the *Bacteriology and Surgery of Chronic Arthritis and Rheumatism*.[1] Figs. 1, 2, 3 and 4 will give some slight indication of the extraordinarily varied and different forms

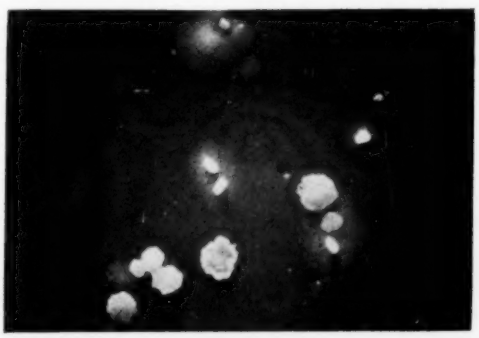

Fig. 2.—Also a culture from feces showing several different varieties from a case of arthritis.

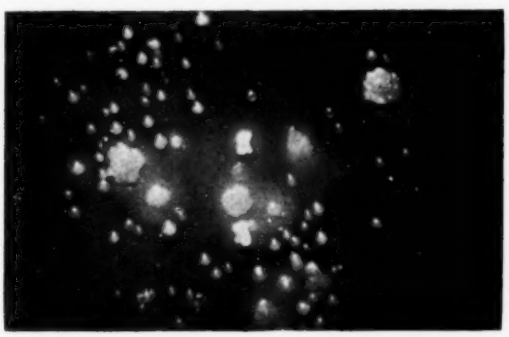

Fig. 3.—Primary culture from a tooth showing many different varieties of streptococci.

of streptococci which can be cultured from a specimen. As an example of a relapse occurring due to reinfection by a fresh organism—a patient who had a severe rheumatoid arthritis (atrophic) after a long period of treatment made a remarkable recovery, and then went to Italy for a holiday. She returned with an extremely severe attack of muscular rheumatism. The stool culture, of which Fig. 4 is a photograph, yielded what was to me an entirely new streptococcus. In the illustration are three of these "walled" colonies touching each other. Following a fresh vaccine of these organisms the rheumatism quickly cleared up.

My method of establishing the identity of a given streptococcus with rapidity and certainty, has led to what one hopes may clarify the whole of animal experiment on chronic arthritis and rheumatism. One has been able

to recognize for certain that the microbes injected into an animal are exactly the same, or different as the case may be, from those which are recovered from that animal. For example, there was found to grow from the roots of many infected teeth, whether from a case of arthritis or from a perfectly healthy person, a streptococcus which fell into my catalog under the number and letter B 7(2)h. The colony on Crowe's medium is perfectly characteris-

Fig. 4.—Primary culture from feces. A case referred to in the text, page 1077.

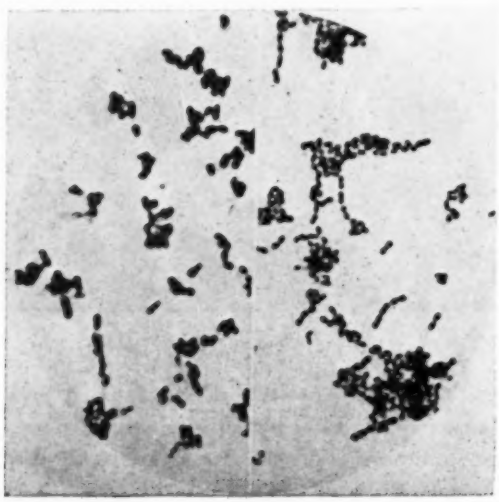

Fig. 5.—Streptococcus B 7 (2) h, magnification by 1700.

tic and recognizable. The sugar reactions are constant: positive to saccharose, lactose, raffinose, and negative to salicin, inulin, and mannite. Milk is always curdled within twenty-four hours. This organism has never been cultured from any other part of the body. When injected into rabbits in small doses, one c.c. of a washed broth culture per 1000 gm. of rabbit, the rabbit usually develops arthritis in one or more of the larger joints, but

whether or not there is a clinical arthritis, the articular ends of some of the bones are in 90 per cent of animals infected by the organism. I have therefore called it osteotrophic. It can be cultured from the bone and but rarely from any other tissue. It produces a granulomatous condition with bony absorption and deposition of fibrous tissue. When recovered from rabbit bone and injected into further rabbits, the process goes on indefinitely, assuming always that the conditions of the experiment are fulfilled, i.e., that the cultures are grown in a suitable medium and are freshly isolated.* Here attention might be drawn to the observations and hypothesis first put forward by Alexander Thompson (Proc. Roy. Soc. Med. **22**: 1119, 1929), that ostearthritis in the human being is essentially a disease of which the primary lesion is

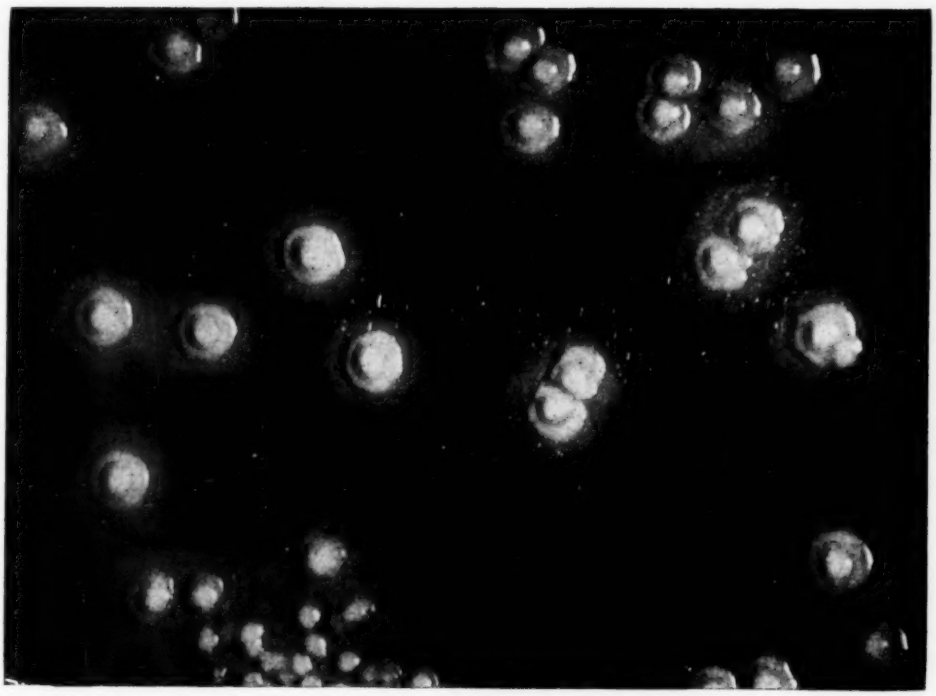

Fig. 6.—Colonies of streptococcus B 7 (2) h, by 20.

cavitation of bone. If that hypothesis is accepted then this condition in rabbits reproduces exactly the human disease. Figs. 5 to 11 show the organism B 7(2)h, cavities in the femur of a rabbit with sections, and for comparison the same apparent lesions in man.

If the view that streptococci are the cause, or one of the causes of chronic arthritis, is correct, it will be agreed that the first condition of successful vaccine treatment is partially at any rate fulfilled when we use a polyvalent vaccine of these organisms.

In my early experience it was, however, borne in on me that streptococci, important though they are, were by no means the only organism in-

*For details of these experiments the original paper in the Annals of the Pickett-Thomson Research Journal, Vol. IV, part 2, should be consulted.

volved in chronic arthritis and rheumatism. I venture here to quote a paper published in 1914 when I first put forward my suggestion that staphylococci were quite as important as streptococci in some cases of chronic arthritis. One of these which belonged to the group of the S. epidermidis albus (Welch), and which I afterward named S. epidermidis albus, variety deformans, was here brought forward tentatively as being the primary cause of rheumatoid arthritis (atrophic arthritis). The reasons for associating this microbe with rheumatoid arthritis seemed to me at the time extremely cogent.

Fig. 7.—Antero-posterior view of the knee joint of a rabbit showing cavitation in the diaphysis of the femur.

"Some three years ago, from the blood of a phthisical patient, who suddenly developed acute arthritis of the left knee joint, associated with brachial neuritis, I isolated a diplococcus, which I have since learned to recognize as the organism here described, the Micrococcus deformans. The case was a remarkable one, for though by no means ill, the patient (a young woman aged thirty-four years) had had for certainty three years previously a raised temperature, which on the rarest occasions dropped below 100° F. night or

morning, and usually remained about 101° F.* Never had it been found to be normal, though two daily observations had been made during the whole of the period. A vaccine prepared from this organism produced remarkable results, in that after a very few doses the knee joint became well and again serviceable, the neuritis disappeared, and the temperature dropped to normal. It was impossible to avoid the conclusion that this diplococcus was causative of the arthritis, the neuritis, and the fever. A year later, within a week of each other, I had the catheterized urines sent me of two women, both suffering from acute rheumatoid arthritis, coming on shortly after parturition. The Micrococcus deformans was found in pure culture and in large numbers in both cases, and in both vaccines of the organism produced that characteristic result which one always associates with the injection of a vaccine pre-

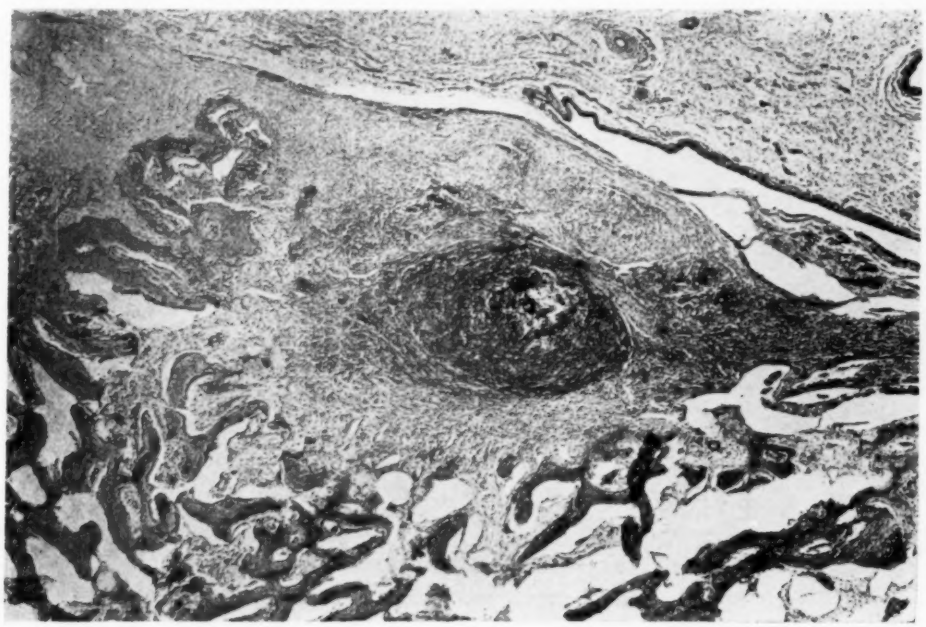

Fig. 8.—Section from femoral condyle of Rabbit 112 infected with streptococcus B. 7 (2) h. There is an abscess in the bone with few traces of bony trabeculae which have been removed almost in toto. Note wide area of polymorphonuclear response and new formation of fibrous tissue. Magnification 45 diameters. Stain, hemotoxylin and eosin.

pared from the organism pathogenic in any given case. About the same time a male rheumatoid patient consulted me. He had a chronic nasal discharge, in which the Micrococcus deformans was found. Still more important, it was present in pure culture in the urine. Here also the effect of a vaccine was obvious. It was already impossible to dissociate rheumatoid arthritis from the Micrococcus deformans."

For further evidence incriminating the Micrococcus deformans, my books should be consulted. The evidence, large as it seems to be, was, however, insufficient to carry complete conviction. Since then, however, further data are to hand in favor of my view.

*This patient had had all sorts of vaccines up to this date without any effect on the temperature.

The blood pathogen selective test shortly to be described, has afforded valuable evidence inasmuch as the bactericidal power of the blood is found to be very low to M. deformans in a large number of patients with chronic arthritis. This observation is quite independent of our clinical experience, which would alone convince anybody who uses vaccines of this organism in the treatment of chronic arthritis.

So far then we have the evidence set forth very sketchily of the connection of a great many varieties of streptococci, and of the Micrococcus deformans, which is probably a modified skin coccus, in the causation of chronic arthritis. There may always be a third type of microbe involved. But if this is so, and clinical results are all against it, it has never yet been found. Certainly some cases are definitely infected with other types of organisms:

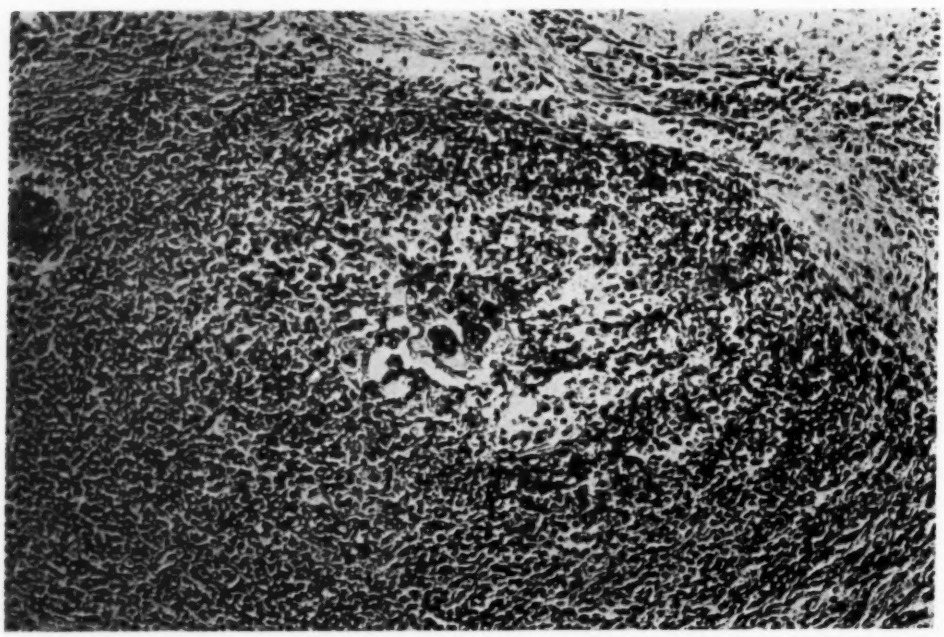

Fig. 9.—Section from femoral condyle of Rabbit 112 infected with streptococcus B. 7 (2) h. Shows abscess in the bone magnified 220 diameters. Note the typical subacute reaction with occasional giant cells.

There are several fragments of bony trabeculae in the abscess, but the bone corpuscles are dead. Stain hematoxylin and mercurochrome.

B. fallax for example (Mutch). Occasionally also B. coli seems to be an infecting organism. Much light has recently been thrown on the systemic infection with aberrant microbes by the work of Cronin Lowe following Solis Cohen.* Pathogen selective tests whereby the patient's own microbes are

*To perform the pathogen selective test, materies morbi obtained from the patient is suitably diluted. Feces are emulsified in saline and diluted until faintly opalescent. Scrapings from infected teeth are ground up in saline and centrifuged, the upper portion being used for the test. Nasal mucus and sputum are treated similarly. Urine can be centrifuged and the deposit used. A microbial culture can also be diluted down for the test.

The essential feature of the test is that the patient's blood should be mixed with small amounts of the products thus prepared before it has time to clot. In practice, 0.1 c.c. of the microbe containing fluid is placed in the bottom of a test tube. Five c.c. of the patient's blood freshly drawn, is added. The whole is then shaken up and placed in the incubator over night. The next day the serum is planted out on a culture plate. Any organism which grows out in pure culture is then pathogen selected.

grown in their own blood, will frequently discover to the observer some microbe hitherto unsuspected in the case.

In regard, then, to the extremely complicated bacterial flora, which is almost certainly involved in the chronic rheumatic diseases, we shall not be surprised at the many failures which have occurred; we shall rather wonder that in the early days of vaccine treatment any cases at all were sufficiently successful to encourage further trial.

Having thus discussed the first two conditions of successful vaccine therapy (for the second condition, i.e., that the organism shall be able to be cultured, is broadly speaking fulfilled by the fact that it can be isolated), we are now in a position to decide exactly what type of vaccine should be injected in any given case. If it be allowed that theoretically a polyvalent streptococcus vaccine is indicated, it follows that with this a vaccine of any other infecting microbe must also be given, and experience has taught that in every case vaccines both of streptococci and of M. deformans *must* be used. An extreme case of what happens if they are not is shown by the following example.

A woman whose periods had recently ceased was sent to me suffering from ostearthritis of the knee joints, a perfectly typical case of so-called menopausal arthritis. Many of the teeth were infected. Probably in consequence she was extremely sensitive to vaccine. There seemed here no indication for anything but streptococcus vaccine and this *alone* was used.

After a course of treatment the teeth were extracted and very good reports of the patient's progress were received. Some fifteen months later the patient was said to be relapsing and came to see me. The knee joints were now found to be completely normal and gave no symptoms of any kind, but pain and weakness had developed in the hands and feet. The neck creaked. The complexion had become dusky. In fact the patient presented all the classical signs of early rheumatoid arthritis.

One felt that had M. deformans vaccine been used all along, combined with the streptococcus vaccine, this misfortune would not have occurred. That the new symptoms were due to M. deformans infection was shown by the fact that the patient's own blood had lost all bactericidal power to this organism (pathogen selective test), and a further indication was obtained from the considerable focal reaction which followed the *first* dose of M. deformans vaccine. This dose was 50,000.

This case brings strikingly before us the essentially mixed character of the infection in the majority of cases of chronic arthritis. Can we in any way collate the character of the lesions with the main type of infection? It has already been seen that the M. deformans was first associated with rheumatoid arthritis or the atrophic arthritis of American writers. I find this definitely confirmed by the pathogen selective test of which I have now carried out some 250. If the M. deformans is the primary cause of this disease, none the less streptococci are usually active as a secondary infection. In hypertrophic or ostearthritis on the other hand, streptococci are the primary infection and in most cases M. deformans is secondarily involved. This leads us

to a simple and natural classification on bacterial grounds—atrophic arthritis, hypertrophic arthritis, and mixed arthritis (when the infection is about equal and lesions of both diseases appear side by side). But the reader may ask what of menopausal arthritis, malum coxae senilis, metabolic arthritis dependent on endocrine, usually thyroid dysfunction. In all seriousness I must state my conviction that these differ only in degree and not in kind. They are all bacterial, and *equally amenable to vaccine treatment*. The meno-

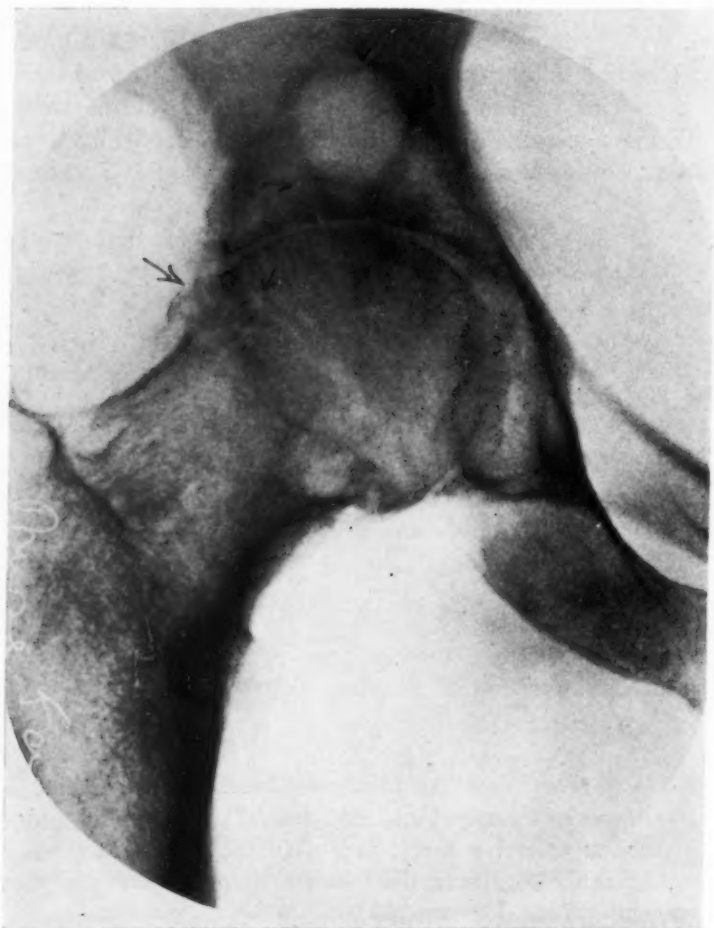

Fig. 10.

Figs. 10 and 11.—Radiographs of hip joint showing similar cavitation in man.

pause is a period of lowered resistance in the first, age with or without trauma determines the second, while in the third the internal glands are themselves probably the victims of the same bacterial invasion.

We are now in a position to assess some of the causes of previous failures in the vaccine treatment of chronic arthritis. The first is because the staphylococcus, M. deformans, has not been used and incorporated in the vaccine. The second reason is that the vaccines used have not been sufficiently

polyvalent. But there is a third reason, which is that the dosage has been absolutely and entirely incorrect and given on entirely wrong principles.

There are two methods of therapeutic inoculation. The one attempts by frequently repeated and rapidly increasing doses to raise the blood immunity, and in the result it renders the cells of the body less sensitive to protein (microbial or otherwise), which is the cause of the symptoms. The other by infrequent small stimuli has for its object the incitement of the system to keep the immunity mechanism in a state of activity. Much of the difficulty and uncertainty as regards dosage and interval has arisen because of the

Fig. 11.

failure to recognize the essential difference between those conditions which are suitable respectively for the exploitation of these two methods. Where the poisonous substance is extraneous to the system as in hay fever, obviously desensitization by rapidly increasing frequent doses should be the method of election, and probably equally so when the offending protein, although issuing from some part of the body, produces its symptoms by its allergic action on some other part. As an example, certain asthmatic paroxysms are produced by the patient's own otherwise harmless intestinal streptococci.

When, however, the system is sensitive in respect of microbes which are present actually in the lesions which we are trying to cure, then the attempt

to desensitize is wrong, for even should it succeed in producing a toleration of large doses, the treatment has failed the more as the microbic infection in the lesion no longer excites the response of the system, nature's attacking power is not aroused, and all barriers against extension to other parts are removed. This seems the most adequate explanation of a number of clinical results which have come under my notice, where sensitiveness disappeared under large doses and extension of the disease followed.

Here then is one of the reasons of Koch's failure with tuberculin. He attempted by frequent and increasing doses to establish a solid immunity. Apart from the excessive autoinoculation already mentioned, the method was bound to fail in the majority of cases, since desensitization to the tubercle bacillus means in fact the suppression of those stimuli from the lesion itself which evoke the active resistance of the system. Unfortunately the medical profession is traditionally imbued with Koch's methods, based on the idea that blood immunity was the goal of our endeavors. In effect, he taught that the bigger the dose the better the result. This false principle which, as has been shown, does not and cannot apply either to tuberculosis or to the chronic rheumatic diseases, must be discarded and replaced by the exact reverse, which may be thus stated: *The smaller the dose the better the result, providing always that some recognizable effect follows.* The treatment by vaccines of rheumatism should proceed on the plan according to which small stimuli are given, each one being allowed to achieve its full effect both in action and in time, before another injection is given. We revert then to the third conception of immunity previously mentioned, and it is this which must govern our treatment. We must stimulate a mild cellular antibacterial activity.

Apart from the reasons above adumbrated, the only evidence which I can bring forward for the correctness of this principle is in the result. In practice the method which best serves our purpose is first to find a dose of streptococcus and of M. deformans which, either separately or combined, produces no reaction whatsoever in the patient, but only an improvement, and to work from that basal point. Secondly, to recognize that reactions are always harmful. They *may* not produce any permanent damage, but the risk is always there. And lastly, that the interval between the doses should depend entirely on the length of time which is covered by the period of improvement. Doses may have to be as low as 1000 organisms. Many cases will occur in practice in which 1000 organisms given once a week lead slowly to cure.

The experiments of Hitchcock, Swift and others rather suggest that chronic arthritis, fibrositis, and in fact all rheumatic manifestations are really allergic in character, and that actual living microbes are not directly involved in the lesions, but that these are present only at the focus of infection.

The explanation of the character of the disease would then run somewhat on these lines: a focus of infection, say infected teeth, a chronic lesion in the appendix, prostate, uterus, tonsil, gall bladder, or elsewhere, is constantly or intermittently draining small amounts of toxin into the blood stream. As a result certain tissues become allergic. Symptoms then would

depend on the waxing or waning of the hypothetical toxin. Even the minutest amounts might produce a disproportionate effect through the well-known "hair trigger" excitability of the sensitized cells. It will be seen that the allergic hypothesis postulates first a focus of infection, the removal of which should cure the disease, and second, some degree of allergy in every case. Further as a corollary, complete desensitization should always result in cure or at least definite improvement. None of these postulates can be maintained. (1) In many cases of arthritis, especially those of the atrophic type, no focus can be found, and even when present the literature of the subject is full of instances and statistics showing how frequently the removal of a focus fails to cure. (2) The majority of cases are not allergic, that is to say, small doses of specific antigen do not aggravate symptoms; finally (3) desensitization does not cure and seldom improves.

(1) That a focus cannot always be found need not here be elaborated, as the fact is common knowledge among those who have studied these diseases.

(2) That the majority of rheumatic cases are not sensitive to vaccine at the beginning of treatment is a fact of experience: that some become so later does not affect the question, although it may render their treatment difficult.

Still it is always possible for the disciples of the allergic hypothesis to question the specificity of the antigen used: an attitude difficult to combat. In the following case one would say that the antigen must have been specific, yet from the beginning of the treatment until complete cure no allergic reaction of any kind occurred.

A man aged forty-six years, suffering from an almost crippling degree of fibrositis (without actual joint involvement), was excreting large numbers of two varieties of streptococci in his urine. One of these was "pathogen selected." After six months' treatment the symptoms had entirely disappeared and specimens of urine examined from time to time showed a steady retrogression in the numbers of bacteria until they also disappeared.

(3) Desensitization does not cure. Although the majority of cases are not in any way allergic at the beginning of treatment, yet most of them show some degree of sensitiveness later on. These can sometimes be "desensitized" by pushing the dose regardless of reaction. It is a dangerous thing to do, as the lesions may rapidly extend and in any case this form of desensitization happens only through the ignorance of the practitioner. But for the purposes of argument the result of excessive dosage is valuable: the disease steadily progresses although large doses, hundreds of millions, are being injected at regular intervals.

The rival hypothesis to the allergic is much simpler and seems more tenable, viz., (1) that the lesions are due to a definite microbic invasion of the areas affected; (2) that these microbes are the "domestic" streptococci and staphylococci of the patient, which may or may not be ensconced in some "focus of infection," and (3) that on account of their lower virulence, the tissues are more or less insensitive to their presence, nor do the microbes usually do much harm beyond provoking some reactive fibrositis. This, as Pemberton has shown, means that chill and damp by lowering the local metabolic rate, will induce twinges of rheumatism. When, however, these domestic

microbes become excessively numerous, there follows a progressive low, reactive inflammatory condition, which constitutes the condition we know as fibrositis or chronic arthritis. If the system reacts strongly to the invasion, then the condition becomes more painful and acute.

How far rheumatism is inherited remains a moot point, but on the analogy of that very similar disease tuberculosis, one would suspect that a certain type of soil was more susceptible. That "arthritis" can be "caught" is probable and may account partly for familial recurrence. A clear case recently came up for treatment when a woman had for two years nursed a case of severe arthritis, and then although up until that time nonrheumatic, she was developing exactly the same type of lesions as her patient.

The technic of the treatment of chronic arthritis by vaccines, with which this article is concerned, is based on the simple hypothesis of the direct invasion of the tissues by the microbes of the disease, that these microbes are streptococci of many different varieties, but always *nonhemolytic* varieties, and staphylococci of one or at most two types, while occasionally but rarely other infecting organisms may play a part.

I am not here proposing to do more than sketch out in very rough outline the treatment in practice, as this is fully described in my *Handbook on the Vaccine Treatment of Chronic Rheumatic Diseases* (Oxford Medical Publications, 1930). In this book, three alternative methods are given. The first is that in use as a general routine at the Charterhouse Rheumatism Clinic, where stock vaccines alone are used, and patients are seen and injected once a week. The second is somewhat simpler and is also suitable for large scale work, whereas the third is more elastic as befits private practice, where autogenous vaccines are prepared after full bacteriologic examinations.

The reader will have gathered already that the principles underlying the method here put forward are entirely opposed to those ordinarily followed. The idea that "the bigger the dose the better the result" must be entirely discarded. Our object is not to attempt to produce a "solid immunity" but to stimulate the individual tissue cells by the smallest possible effective doses, to bring into action their antibacterial mechanism, without subsequent depression of that mechanism. Since the effect of a general "reaction" is temporarily at least to depress the antibacterial activity of the whole system, such reactions are to be avoided. It is therefore very necessary to get a clear picture of what is meant by reaction. Reaction is of three distinct kinds: local, focal, and general. The first of these practically never occurs with streptococcus or M. deformans vaccine if the injection is given subcutaneously. A focal reaction is indicated by increased symptoms in the disease area, e.g., pain or swelling in a joint, muscular spasm, and the like. Unless a focal reaction is excessive, resulting in stasis or acute exacerbation, it does not do much harm, but should be avoided as being unpleasant to the patient, and unnecessary to the "cure." A general reaction on the other hand must be avoided at all costs. Yet a general reaction may be far less irksome and only noticeable if a careful watch is kept. The signs vary from severe malaise with headache and temperature to a mild feeling of lassitude or sleepiness, or even only a period of lag before improvement sets in. If a patient is disinclined

for his usual activities or admits to being slightly drowsy within forty-eight hours of the dose, he is suffering from a general reaction. When this occurs, rest is essential and therefore the doses should always be given on such days as will admit of rest on the following day if necessary. Except where general reaction occurs, no change in the patient's activities or way of life is necessary or in fact desirable. Then the idea must be discarded that the actual size of the dose matters in the least, as long as it is the best dose for the patient. It may be lower than 1000 organisms or as high as 1000 million! But much more probably nearer the former. The majority of cases progress steadily on doses ranging from 1000 to 100,000 and but few require more than the higher of these two, except in the very early stages when the majority of patients are insensible. During treatment at least 90 per cent of cases develop some degree of sensitiveness. It is this fact which constitutes the main source of failure. It explains the very frequent statement by patients that vaccine treatment did them good to begin with, but that afterward it seemed to make them worse. At the first hint of the development of sensitiveness, the dose must be drastically reduced and the greatest caution exercised both in size of dose and length of interval. In practice, especially in the earlier stages of treatment, one should make it a fixed rule to reduce the dose to one-tenth of that which is followed by *any sign whatsoever* of a general reaction. A focal reaction demands a drop to half, or if severe to one-fifth, of the exciting dose. During the earlier stages of sensitiveness, doses should not be given more often than once a week, and sometimes a longer interval is even better, especially if the effect of the dose is ambiguous.

When a case of chronic arthritis comes up for treatment, circumstances will decide whether autogenous vaccine is to be given or stock. We will consider an hypothetical case, where full bacteriologic facilities are available, since the actual scheme of dosage is the same.

At the preliminary interview, after entering up the history and result of examination, arrangements must be made for dental radiograms and the collection of specimens of urine (catheter in female), feces (after a purge), posterior nares (if catarrh), etc. Also a tooth must be extracted for culture purposes if dental sepsis is present.* Pathogen selective blood tests are also made. It is advisable to start the treatment by some doses of stock vaccine to test the tolerance of the patient. In this way also no time is wasted. The treatment should begin with an injection of 100,000 polyvalent streptococcus vaccine; five days to a week later 100,000 M. deformans† is given. There must follow from one or other or both of these doses, (a) a focal reaction, (b) a general reaction, (c) definite improvement, or (d) no change whatsoever. There are now two distinct lines of advance. (1) To carry on alternating the streptococcus and M. deformans vaccine until we find the reaction point of *each* and then to combine the two together in just that proportion, or (2) to

*For all the details of the bacteriologic and other technic, reference can be made to my books.

†The vaccines used by the author can be obtained from Messrs. Reynolds & Branson Ltd. 13, Briggate, Leeds.

combine them at once in equal quantities. The amount of the dose is then regulated entirely by the dose of that organism to which the patient is most sensitive. The second method is to be preferred in all cases at the beginning of treatment. Later if difficulty arises the two kinds of vaccine can be tested out separately, but in *no case* must either be entirely omitted.

What now should be the third dose? Let us consider the contingent effects of the first two doses; the following schedule will give the correct procedure.

a. (focal reaction) following either first or second dose,
if slight give { 50,000 streptococci / 50,000 M.deformans
if severe give 20,000 āā.

b. (general reaction) following either first or second dose,
whether slight or severe give 10,000 āā.

c. (definite improvement) following either first or second dose, give 100,000 āā.

d. (nil) following either first or second dose, give 100,000 āā.

After the third dose the autogenous vaccine should be ready and must then be combined with stock vaccine (the latter must never be omittted). Again we assess the next dose from the same considerations as before and so on while the treatments last. Be it particularly noted that the amount of each dose depends on the effect of the preceding dose and on *that alone*.

TABLE FOR THE FOURTH AND SUBSEQUENT DOSES

EFFECT OF FIRST OR SECOND DOSE	THIRD DOSE	EFFECT	FOURTH DOSE
(a) slight	50,000 āā	(a) slight	25,000 āā
		severe	10,000 "
		(b)	5,000 "
		(c)	50,000 "
		(d)	75,000 "
(a) severe	20,000 āā	(a) slight	10,000 "
		severe	4,000 "
		(b)	2,000 "
		(c)	20,000 "
		(d)	30,000 "
(b)	10,000 āā	(a) slight	5,000 "
		severe	2,000 "
		(b)	1,000 "
		(c)	10,000 "
		(d)	15,000 "
(c)	100,000 āā	(a) slight	50,000 "
		severe	20,000 "
		(b)	10,000 "
		(c)	100,000 "
		(d)	150,000 "
(d)	100,000 āā	(a) slight	50,000 "
		severe	20,000 "
		(b)	10,000 "
		(c)	100,000 "
		(d)	150,000 "

The following is an example in practice of the result of drastic reduction of dose. A patient suffering from a very severe and intractable brachial

neuralgia, with slight nerve tenderness (some neuritis), was quite unable to work. Extreme pain at night prevented sleep. Treatment: stock vaccine once a week.

First dose, 100,000 streptococci.	Pain severe, sleepy, sick. (b)
Second dose, 100,000 m. deformans.	Tired and drowsy. (b)
Third dose, 10,000 āā.	No improvement, out of sorts, pain as before. (b)
Fourth dose, 1,000 āā.	Pain disappeared almost entirely twenty-four hours later. Beginning to recur, after six days.
Fifth dose, 1,000 āā, and so on.	Result excellent.

Compare these doses with those usually sent out by commercial firms, or recommended by well-known authorities. Pemberton, in his last book, gives up to 2000 million at intervals of five to seven days.

Apart from the results of treatment which show that small doses are quite efficient, further justification is to be found in a comparison with the modern tuberculin dosage. Those who give unaltered tuberculin, that is, the bacillary emulsion, use a range of from one to ten millionths of a milligram in children and perhaps five to ten times that dose in adults. The equivalent dose of the cocci which constitute the vaccine for rheumatism, would be for children from one to ten thousand and for adults from ten to one hundred thousand.

Occasionally patients develop during treatment such a marked degree of sensitiveness that even 1000 organisms are not tolerated. Various methods are under trial for dealing with the situation. The simplest is to use benzamine lactate with the vaccine. It is then rendered more tolerable to the patient. A 4 per cent solution of benzamine lactate should be put up in sterile vaccine bottles. This must be combined with the vaccine in such amount that the whole solution injected contains not less than 2 per cent of the drug. It is only necessary to use it where doses of less than 1000 are followed by violent reactions. The vaccine itself should be put up in as small a bulk as possible, so that not more than a total of half a c.c. of 4 per cent benzamine lactate is required.

The rationale of this peculiar character is obscure. Possibly the excitability of the tissue cells is lulled by the anesthetic properties of the drug. Other methods of dealing with the sensitive state are described in my previous books.

The length of the treatment depends on the progress of the "cure" and is extremely variable. There is no fixed term or definite number of doses which constitute a "course." One will keep in mind the general principle that, so long as the injections are found necessary to prevent relapse, they should be continued.

The matter is easily put to the test. The patient is merely directed to wait until symptoms tend to recur before coming back for his dose. In time it will be found that even with quite small doses, once a fortnight will be

sufficiently often to keep down all signs of rheumatism, and later that for three weeks or longer no injection is required.

The age of the patient has a considerable bearing on the question. Young people, for example, will throw off the infection rapidly and completely unless there is some active focus of infection present. This must be suspected if the patient exhibits undue sensitiveness. Older patients, on the other hand, and those in whom the disease has been of long standing, may never become quite free, and will require a few doses once or twice a year.

In conclusion, I would beg to advance the plea that vaccine treatment should not be used only and as a last resort in advanced arthritis and rheumatism, where crippling deformities may prevent complete functional cure, but that the method should also be adopted in early cases when it is almost invariably successful.

15 PORTLAND PLACE.

THE BIOLOGIC PRODUCTS OF STREPTOCOCCUS CARDIOARTHRITIDIS AND THE LATEST DEVELOPMENTS IN THE TECHNIC OF THEIR THERAPEUTIC APPLICATIONS

By James C. Small, M.D., Philadelphia

IT HAS been nearly four years since the biologic products of Streptococcus cardioarthritidis were introduced in the treatment of rheumatic fever.[1] This period has provided abundant opportunity for observing patients in whom these products have been used during this initial stage in their development. It appeared rather early that the antiserum did not represent a finished therapeutic agent which could be used successfully in treatment unless certain imperfections of it were appreciated. A technic in its application had to be developed with a view of minimizing the untoward effects likely to arise because of these imperfections. This technic differs in several important particulars from the usual technic of antiserum therapy.

The attempts to supplement the treatment with antiserum with that of a bacterial vaccine prepared from Streptococcus cardioarthritidis very early revealed the dangers of using such a vaccine in dosages commonly employed in vaccine therapy, and after repeated reductions in dosage of the vaccine, eventually led to the preparation and use of a normal saline extract of the streptococcus. This product, designated a soluble antigen of Streptococcus cardioarthritidis, is a new and very potent agent in biologic therapy. The attempts to develop a technic in its application which would be most efficient have continued since January, 1928. The result has been that much has been learned of the unusual characters of this product, and the technic in its application has been developed after much trial and error. This technic is not to be regarded as perfected so that those who undertake to use this agent in treatment should be ever alert to any future developments and ever ready to modify their methods accordingly.

Since both the antiserum and the soluble antigen of Streptococcus cardioarthritidis are being used rather widely and after methods which do not take into account the more recent developments in the technic of their applications,[2] it is deemed important to record what our intensive study of these agents has revealed to date of their properties, and of the most effective methods in their application.

THE "FOCAL REACTION" FOLLOWING LIBERAL AMOUNTS OF THE ANTISERUM OF STREPTOCOCCUS CARDIOARTHRITIDIS AS AN EVIDENCE OF ITS PRESENT IMPERFECTION

In using the antiserum, a most important consideration is that of avoiding certain deleterious effects associated with the employment of dosage which is too liberal in amount. This has been designated the "Focal Reaction"[3] and described in early publications. Its harmful effects are particularly observed in

patients acutely and gravely ill with rheumatic fever, who are also the patients in whom one is inclined to employ the largest amounts of antiserum. The outstanding clinical features of the "focal reaction" are an actual extension of the acute arthritis, a marked increase in the leucocyte count, and a continued elevation of temperature. The extensions of the acute arthritis are particularly prone to involve the small joints of the fingers which become swollen and the skin over them reddened. Usually the pain and tenderness is much less than one would expect from the angry appearance of the joints. With this reaction the leucocyte count is very markedly elevated; counts of 30,000 to 40,000 per c.mm. are common in patients who showed counts of 15,000 to 20,000 prior to the onset of the reaction. A leucocyte count as high as 70,000 has been observed in this reaction. The temperature during the focal reaction may rise slightly above the high points recorded prior to its onset but does not tend to show the remissions ordinarily so characteristic of rheumatic fever except toward the end of the reaction period when daily fluctuations are noted. Very careful discrimination and some experience with the more severe forms of this reaction are necessary in order to differentiate it from the spontaneous extensions of the disease. Severe reactions may last for twelve to fourteen days, but a period of from five to eight days is more common. They may be terminated promptly by adequate administration of salicylates for one or two days only and the symptoms do not tend to recur after this medication is discontinued abruptly.

This type of reaction is not prominent following the use of antitoxic serum in diphtheria and tetanus. A theoretical explanation of it[3] has been suggested based largely upon the facts developed by Swift and his coworkers[4] which have demonstrated that certain protein products of streptococci are potent antigens for inducing hypersensitive states in animals. Since hypersensitive states induced by bacterial protein can be transferred passively,[5] it was suggested that the "focal reaction" in patients treated with the antiserum of streptococci represented the aggravation of certain allergic symptoms of the disease which was brought about by the transfer to the patient of the antibodies of these protein factors of streptococci contained in the antiserum used for therapeutic purposes. It was pointed out further that this condition might also be expected to apply in cases of other antistreptococcal sera prepared by the method of injecting animals with the whole bacteria rather than with their toxins only. The antiprotein antibody would appear in an antiserum as a separate and distinct antibody from any antitoxin. The former is not species specific; the latter is species specific. The removal of the antiprotein antibody without affecting the species specific antitoxin content of such a serum has been suggested as the outstanding requisite[3] for perfecting it as a therapeutic agent. We believe, therefore, that before the specificity of any antistreptococcus serum can be established beyond doubt in rheumatic fever, this separation of antiprotein antibody from the bacterial species specific antibodies must be effected.

The following selected case history presents many of the features of a severe "focal reaction" which was allowed to run its course without salicylates. Morphine or codeine was used as required to provide relative comfort for the patient.

CASE 1.—J. W. Admitted Dec. 31, 1927, discharged Feb. 1, 1928. Colored, female, aged twenty-four years, domestic. Diagnosis: acute rheumatic fever.

Following an acute upper respiratory infection, this patient began six days before admission to have pain in the right hip, and pain, swelling, and tenderness in the left ankle, left foot, the right ankle, and the knees. She had no previous attacks similar to this but three years ago she had pain and stiffness in the right hand and wrist lasting only three or four days. She has had "colds" frequently and "sore throat" occasionally. At the time of admission there was pain, swelling, and tenderness in both knees, and stiffness in the right hip. The patient appeared toxic, and there was profuse sweating. The conjunctivae were moderately injected; the tonsils were enlarged and the whole pharynx hyperemic. The submaxillary glands were enlarged but not tender. The pulse rate was 120 per minute, and the temperature was 101.2° F. The pulmonary areas were clear. The cardiac apex impulse was in the fourth interspace and 10 cm. to the left of the midsternal line. There was a palpable thrill over the apex, and a rough systolic murmur over the mitral area. There were no signs of cardiac decompensation. The liver and spleen were not enlarged or tender.

Laboratory Findings—

Blood count, leucocytes 11,000 per c.mm.
Blood culture, sterile.
Blood urea nitrogen, 17 mg. per 100 c.c. blood.
Blood Wassermann: cholesterinized antigen, plus four;
acetone insoluble antigen, negative.
G. C. complement fixation, negative.

The patient received by intramuscular injection 20 c.c. of the concentrated equine antiserum of Streptococcus cardioarthritidis* on Dec. 31, 1927, and an additional 20 c.c. on Jan. 1, 1928. Salicylates were not administered. Codeine was used as required for symptomatic relief.

The summary below presents daily records of the condition of the joints, the maximum and minimal pulse rates and temperature readings, the opsonic index for Streptococcus cardioarthritidis of the patient's serum, and the leucocyte counts. The extension of the acute arthritis, the continued elevation of temperature without the characteristic daily fluctuations, and the marked increase in the leucocyte count are characteristic of the focal reaction which in this case lasted for about ten days.

THE TECHNIC OF TREATMENT WITH ANTISERUM OF STREPTOCOCCUS CARDIOARTHRITIDIS

With this imperfection existing in the antiserum of Streptococcus cardioarthritidis recourse was taken to methods in its clinical application which, until such time as the imperfection of the serum could be eliminated, would be helpful in preventing the more severe forms of the "focal reaction."

The procedures found to be of greatest value were:

1. A reduction of the dosage of antiserum to the estimated minimal requirements of the patient.

2. The administration of the estimated total dosage in divided amounts allowing an interval of eighteen to twenty-four hours between the several injections.

3. The use of moderate doses of salicylates for the few days only during which the antiserum was being administered.

This technic of treatment with antiserum differs rather radically from the usual procedure in the administration of a therapeutic antiserum—the keynote of which is prompt administration of liberal dosage. Such should also be the

*The biologic products of Streptococcus cardioarthritidis used in the patients cited in this communication were provided through the courtesy of the H. K. Mulford Company of Philadelphia.

TABLE I

SUMMARY OF CASE 1

DATE	CONDITION OF JOINTS			PULSE RATE	OPSONIC INDEX	TEMPERATURES		SERUM TREAT.	SERUM DISEASE	LEUCOCYTE COUNTS
	PAIN	SWELLING	TENDERNESS			MAX.	MIN.			
12/31/27	B.K.	B.K.	B.K.	90-120		101.2				
1/ 1/28	B.K.	B.K.	B.K.	96-110		102.0	100.2	20 c.c. conc.		11,200
1/ 2/28		B.K.	B.K.	96-110		102.6	99.8	20 c.c. conc.		
1/ 3/28	L.K.	B.K.	L.K.	90-110	1.2	102.4	99.8			14,000
1/ 4/28	R.E.	R.W.	R.E., R.W., L.K.	110-124	0.8	103.2	101.0			20,000
1/ 5/28		L.H.		100-112	0.7	103.4	100.6			11,000
1/ 6/28				96-110	0.9	101.0	100.6			12,200
1/ 7/28	L.W., L.E.	L.W., L.E.	L.W., L.S., L.E.	90-110	1.2	103.4	101.6		+	8,600
1/ 8/28	L.W.	L.W.	L.W.	112-120		102.4	102.0		+	
1/ 9/28	R.E., R.W.	R.W.	R.W., R.E., B.K.	110-130	1.1	102.8	101.6		+	19,800
1/10/28	R.W.	R.W.	R.W., L.K.	120-140	0.8	102.2	100.0			18,100
1/11/28	B.W.	B.W.	B.W.	120-130		102.6	100.2			10,600
1/12/28	L.W.	B.W.	L.W.	110-140		102.6	100.2			
1/13/28	L.W.	B.W.	L.W.	112-134	0.6	102.2	99.6			
1/14/28		B.W.	L.W.	114-130		101.6	99.4			
1/15/28	L.W.	L.W., R.W.	L.W.	100-130		102.4	99.0			
1/16/28				104-120	0.9	102.4	99.2			
1/17/28				110-120		98.6	98.4			

B. K. both knees; L. K. left knee; R. E. right elbow; R. W. right wrist; L. E. left elbow; L. W. left wrist; L. S. left shoulder.

method of choice in the use of antistreptococcal serums if it were not for the fact that in their present stage of development they are prone to set up the undesirable "focal reactions" and therefore cannot with expediency be used in as liberal amounts as would be most desirable. This serves to emphasize the twofold nature of the problem—that of perfecting an antiserum and that of developing a technic of its application. The latter is most important in the present stage of development of this antiserum, and may be outlined briefly as follows:

1. The total dosage recommended in the treatment of a patient with acute rheumatic fever is 5 c.c. of the concentrated equine antiserum per one hundred pounds of body weight except when the patient weighs less than one hundred pounds when 5 c.c. is regarded as the minimal effective dosage. With the unconcentrated bovine antiserum a volume dosage of 20 c.c. is regarded as the equivalent of 5 c.c. of the concentrated equine antiserum.

2. The antiserum is injected intramuscularly (never intravenously) using 40 per cent of the total estimated dosage as the first injection, which is followed after eighteen to twenty-four hours by a second injection of the remaining 60 per cent. Occasionally where a partial response only is adjudged as being obtained following the second injection, a third injection equal in amount to that of the second may be practiced on the third, or fourth day, but no injections thereafter are recommended.

3. Sodium salicylate, or its equivalent in related compounds, is administered in daily amounts of sixty to eighty grains from the beginning of the administration of serum and continued until twenty-four hours after the last injection of antiserum, whereupon it may be discontinued abruptly.

The following selected case history represents a patient in whom small doses of antiserum were used. Salicylate medication was not used in this patient in conjunction with the serum treatment. From the history, this patient had been receiving salicylate medication up to the time of admission to the hospital, and it is probable that this may account for the absence of leucocytosis on admission.

CASE 2.—F. R. Admitted April 10, 1928, discharged May 4, 1928. White, male, aged nineteen years, baker. Diagnosis: acute rheumatic fever.

Two weeks prior to the onset of the acute arthritis of rheumatic fever this patient suffered an attack of acute upper respiratory infection which was diagnosed "la grippe." He had never had a previous attack of rheumatic fever but had suffered occasional attacks of tonsillitis. The acute arthritis first appeared in the right ankle, and later involved the left ankle, and both knees.

At the time of admission the patient was suffering from acute pain in the right wrist, left knee, and right ankle. These joints were swollen, very tender, and the skin over them was reddened. There was also tenderness and pain on motion in the left wrist, right knee, right elbow and right shoulder. The patient appeared very toxic. The skin was moist and pallid. The pulse rate was 100 per minute and the temperature 102° F. The tonsils were enlarged and cryptic but not acutely inflamed. The lung areas were clear. The cardiac apex was in the fourth interspace, 9.5 cm. from midsternal line. The right border was at the right sternal margin. A slight thrill was noted over the apex as was also a soft systolic murmur, transmitted to the left axilla. The second sound at the pulmonary auscultation area was accentuated. There was no tenderness over the abdomen. The liver and spleen were not palpable.

TABLE II

PROGRESS RECORD OF CASE 2

DATE	CONDITION OF JOINTS			PULSE RATE	OPSONIC INDEX	TEMPERATURES		SERUM TREAT.	SERUM DISEASE	LEUCOCYTE COUNTS
	PAIN	SWELLING	TENDERNESS			MAX.	MIN.			
4/10/28	R.W., L.K., R.A.	R.W., B.K., R.A.	R.E., B.W., B.K. R.A., R.S.	98-118	0.5	102.0	100.0	5 c.c. (conc.)		8,000
4/11/28	R.W.	R.W., L.K.	R.W.	90-104		102.4	100.8	5 c.c. (conc.)		14,200
4/12/28	R.W. (slt.)	R.W., L.K.	R.W., L.K.	90-108	0.9	102.0	100.0			10,400
4/13/28		R.W.	R.W.	84-102	1.6	101.0	99.6			14,200
4/14/28		R.W.	R.W. (slt.)	84- 98	1.0	101.8	98.6			10,000
4/15/28		R.W.	R.W. (slt.)	72- 94		99.4	98.4		+	
4/16/28		L.W. (slt.)	L.W., L.H.	78- 90		98.8	98.2		+	8,600
4/17/28				80- 88	1.4	98.6	98.4		+	8,100
4/18/28				80- 92	1.3	98.6	98.0			9,800
4/19/28				80- 86	1.2	98.6	98.2			7,600
4/20/28				70- 82	1.1	98.4	98.4			7,000
4/21/28				76- 94		98.8	98.4			8,200

R. W. right wrist; L. K. left knee; R. A. right ankle; B. K. both knees; R. E. right elbow; B. W. both wrists; R. S. right shoulder; L. W. left wrist.

Laboratory Findings—

Urine: Amber color, acid, specific gravity 1.030, no albumin, no sugar, no casts; epithelial cells and a few leucocytes noted.

Blood count: Hemoglobin 14.9 gm. per 100 c.c.; erythrocytes 4,700,000; leucocytes 7,300; polymorphonuclears 68 per cent; lymphocytes 32 per cent.

Blood urea nitrogen 12 mg. per 100 c.c. blood.

Blood uric acid 3.6 mg. per 100 c.c. blood.

Blood sugar 133 mg. per 100 c.c. blood.

Blood culture, sterile.

Throat culture, Streptococcus cardioarthritidis.

Blood Wassermann, negative.

Patient's serum up to dilution of 1:80 agglutinated suspensions of Streptococcus cardioarthritidis, and the opsonic index with this streptococcus was 0.5.

This patient received by intramuscular injection 5 c.c. of the concentrated equine antiserum of Streptococcus cardioarthritidis on April 10, 1928, and an additional 5 c.c. on April 11, 1928, or a total dose of only one-fourth that used in Case 1.

The progress record (Table II) contrasts sharply with that of Case 1, in that a "focal reaction" did not develop. The prompt rise of the opsonic index for Streptococcus cardioarthritidis with the clinical improvement is characteristic of the value of this test in practice.

THE DEVELOPMENT AND USE OF AQUEOUS EXTRACTS OF STREPTOCOCCUS CARDIOARTHRITIDIS

Appreciating the persistent character of the lesions of rheumatic fever as they occur in the blood vessels and the heart, it is scarcely to be expected that any antiserum which at best confers protection over a period of weeks, would alone constitute an adequate treatment. It appeared desirable to attempt to supplement any passive protection conferred by antiserum, by inducing, if possible, an active immunity from the use of bacterial vaccines, or products of a related nature. It also was regarded as important to begin these attempts as soon as appeared feasible after the use of antiserum in order to induce some degree of active immunity before the period of passive protection provided by antiserum had terminated.

With bacterial vaccines as ordinarily employed, difficulties were encountered from the very beginning. Relapses apparently associated with the injections of vaccine occurred with doses as small as 10,000 of the devitalized streptococci. This unfavorable experience very early led to the development of aqueous extracts of the bacteria in order that dosage might be still further reduced. Thereafter we met with failures intermixed with apparent success through a period during which dosages were being constantly reduced, until the present time when such minute amounts of the aqueous extract of Streptococcus cardioarthritidis are being used that they can scarcely be regarded as capable of inducing an active immunity after the manner of a bacterial vaccine. Our best results with these aqueous extracts of streptococci are our latest results. After working with them and studying carefully the responses of many patients over a period of more than two years, it is more than ever apparent that we have only touched upon their possibilities in therapy, and further, that the dosages and methods of administration as developed to date do not represent perfection. The present dosages and the technic of their employment are safe, and yield therapeutic results which cannot be obtained with bacterial vaccines, but we do

feel that more prompt and striking results with these extracts are yet to be obtained upon learning more of the manner in which they act and upon further development of the technic in their application.

The four dilutions of these aqueous extracts of Streptococcus cardioarthritidis now in use contain respectively per cubic centimeter, the water-soluble materials of 0.1; of 1; of 10; and of 100 streptococci. They have been designated soluble antigens of Streptococcus cardioarthritidis and the dilutions above mentioned are referred to as 1:1 billion, 1:100 million, 1:10 million and 1:1 million respectively. Our experience in the beginning with dilutions of 1:10, 1:100, 1:1000, 1:10,000, and 1:100,000 was unsatisfactory, in that activation of symptoms frequently occurred while patients were under treatment with subcutaneous injections of amounts ranging from 0.05 c.c. to 1.0 c.c. Wilson[2] in a recent article records a few patients in whom she employed the soluble antigen of Streptococcus cardioarthritidis in dilutions of 1:100 and 1:1000. These dilutions were those used for a brief period very early in our work but are stronger than those recommended in my first publication on the use of antigen in May, 1928, and much in excess of recommendations issued in form letters of December 12, 1928, to those to whom the antigen was furnished for clinical trials, when the dilution of 1:100 millions was already arrived at in the development of this method of treatment. The high percentage of relapses in her patients while under treatment with the dilutions used serves to indicate the danger attending the use of excessive dosage and demonstrates how readily one may nullify the effects of antiserum by a supplemental course of the antigen employed in dosages which are too large. Yet these disastrous effects of antigen are so subtle that even such a capable clinician as Wilson failed to incriminate it as playing a part in the relapses noted in her cases. The reasons for this will appear under the discussion of the reactions following the use of the soluble antigen.

REACTIONS FOLLOWING INJECTIONS OF SOLUBLE ANTIGEN OF STREPTOCOCCUS CARDIOARTHRITIDIS

As between the antiserum and the soluble antigen of Streptococcus cardioarthritidis, the latter is by far the most difficult to apply clinically. Progress in its development for clinical use was made only through trial and error. The errors have been largely from the use of overdosage. This will be readily understood when it is appreciated that the adjustment of dosage downward soon reached amounts so minute as to be entirely new in any form of biologic therapy. It is very difficult to conceive of any effect whatever as being produced in patients by a fractional part of the extract of a single streptococcus and yet the extensive use of the extract has amply demonstrated that very marked reactions in patients with rheumatic fever, and in patients with chronic atrophic and hypertrophic arthritis, may follow injections of such minute amounts. Reactions following dosage as minute as this suggest an extremely hypersensitive condition on the part of these patients.

The fact that patients with chronic arthritis appear as hypersensitive to this product, as do those with rheumatic fever has favored its study in patients by providing an abundant supply of clinical material in which a standardiza-

tion of dosage could be practiced with safety. Such procedure is not practical in patients with rheumatic fever because of the dangers of activating the serious cardiac lesions by overdosage. A further advantage in chronic arthritis, especially in the atrophic type, was provided in the superficial character of the lesions in the joints so that any activation or subsidence of the inflammation could be studied objectively in them.

A disadvantage in using this type of patient for study arises because of the spontaneous activation or subsidence of signs of inflammation about the joints under a great variety of influences entirely beyond experimental control. It has therefore been necessary to study the clinical effects of injections of this antigen in a very large number of patients. Based on experience of this kind, the following may be stated as our experience to date.

The reactions following the injections of antigen may be classified in order of their frequency of occurrence, as:

I Focal II General III Localizing IV Local

I. The focal reaction occurs constantly with proper dosage. It consists of an activation of both the objective and subjective symptoms attending the joints involved in the arthritis. Frequently joints which have been quiescent for months will show activity as well. Myalgias and neuralgias are also frequent manifestations in this type of reaction. The most severe focal reactions occur with the secondary phase of the general reaction described below.

II. The general reaction is biphasic when excessive dosage is used, but with the smaller more properly adjusted dosage, the primary phase of the reaction is not noted, only the secondary phase appearing. The primary phase usually appears within the first twelve to eighteen hours and may continue from six to twenty-four or more hours. Extreme lassitude and malaise with drowsiness followed by wakefulness are outstanding manifestations of this phase of the general reaction. The tendency is for the blood pressure to be reduced, and the pulse to be accelerated. A slight rise of temperature occurs at times in afebrile patients and more commonly in febrile patients. Little change or only a slight aggravation of the arthritis occurs with this phase. This phase is followed by a period of euphoria which may extend over two or three days, during which the patient experiences relative comfort in the joints and is greatly encouraged. Following this, the secondary phase comes on gradually with a return of all the arthritic symptoms and characterized especially by marked tremulousness, nervous excitability, emotional depression, irritability, anorexia, nausea and occasionally vomiting, a cool moist skin, slow pulse, lowered blood pressure, and a tendency to a subnormal temperature.

The primary phase of the reaction is aggravated by the injection of more antigen and is associated with overdosage. The secondary phase of the reaction is promptly alleviated by the injection of more antigen. This relief occurs within two hours after subcutaneous injections, and has been observed to appear eight minutes after intravenous injections. The primary phase of the reaction should never be produced with dosage properly adjusted to the patient and the secondary phase should be anticipated by a repetition of the injection. This ideal condition constitutes the greatest difficulty in practice because we have

at present no means of anticipating how the patient will react and each patient must be subjected to trial with minute dosage, and adjustments made as soon as possible upon observing his reactions. For the best clinical results these adjustments should be made as speedily as possible to a dosage so small that the patient will be maintained either in the euphoric stage or, better still, to a dosage so small that only the mildest symptoms of the secondary phase of the reaction appear within several hours after the injection. Certain peculiarities arise here which have not been met in any other form of biologic therapy, and should be emphasized even though they cannot be explained in the present state of our knowledge.

Gross overdosage with antigen does not increase the severity of the symptoms of the general reaction, it merely delays their appearance and prolongs the duration of the several phases of the reaction. A patient may continue in the primary phase of the reaction, which is very difficult to recognize as such, for from eight to fourteen days following a single injection of, for example, 0.05 c.c. of a 1:1000 dilution of antigen and without any period of euphoria, before the easily recognized secondary phase appears, whereas, 0.05 c.c. of a dilution of 1:100,000,000 may produce no symptoms of the primary phase but an immediate period of euphoria lasting from four to eighteen hours after which a very sharp and stormy secondary phase will appear. In the first instance the patient without further treatment may continue for two or three weeks in an active cycle of arthritis before it subsides to the preinjection level; in the latter case, the symptoms of the secondary phase may continue for a few days only, after which the arthritis may or may not be less troublesome than before the injection. It is difficult to associate any reaction with the larger dosage because the symptoms appear so late and come on gradually. The reactions following the smaller dosage are more easily associated with its injection because they come on more promptly and the symptoms are more stormy in character. This condition of affairs constitutes an apparent paradox which has been discussed from a theoretical standpoint in a recently advanced hypothesis.[3]

A patient upon being started in this treatment with a very minute dose may show neither a primary phase nor a period of euphoria, but an immediate reaction of the type of the secondary phase. This has been observed to come on within fifteen minutes after an intravenous injection of 0.1 c.c. of a special dilution of 1:100 billion and to last for three and one-half hours when the symptoms of it terminated very abruptly. While the very unusual character of these responses cannot be explained, the facts observed in practice are clear and may be restated in the generalizations:

1. Large doses of antigen are followed by indefinite reactions, greatly delayed in their appearance and very prolonged in duration.

2. As the dosage is regulated downward the time elapsing between its injection and the appearance of the primary phase of the reaction is shortened, then this phase fails to appear, being replaced immediately by the period of euphoria and lastly the period of euphoria fails to appear but instead a prompt and sharp reaction of the type of the secondary phase. Following repeated injections of the infinitely small amounts of antigen eliciting the latter type of reaction, the symptoms on each repetition grow less and finally fail to appear

at all. This appears to be associated with the building of a tolerance because thereafter the dosage may be gradually increased without reactions.

III. The localizing reaction occurs with less consistency than the above described ones. It is a most interesting and helpful phenomenon when dealing with a general disease arising so frequently from closed foci of infection, in themselves so quiescent as to escape clinical detection.

This reaction is an acute activation of inflammation in some quiescent focus of infection which comes on with the secondary phase of the general reaction and is noted most often following the first or second minute trial doses used in beginning a course of treatment. As mentioned these doses are most apt to excite sharp and stormy general symptoms coming on within twenty-four hours after their injection. This reaction has most frequently been seen as the lighting up of acute inflammation in nasal accessory sinuses. In a few instances acute alveolar abscesses about the apices of devitalized teeth, which recent x-ray evidence had not condemned, were most striking instances of this type of reaction.

IV. Local hyperemia at the site of intradermal injections of antigen is noted occasionally. These areas are at their height from eighteen to twenty-four hours after an injection. They amount to faint pink macules, or very slightly raised flat papules, seldom exceeding 1.5 cm. in diameter and typically surrounded by a narrow zone of blanching which merges with the normal appearance of the surrounding skin. These reactions have been noted following the intracutaneous injection of 0.05 c.c. of the 1:100 million dilution. Patients showing these reactions do not appear to differ in their general hypersensitiveness, as judged from the other reactions, from patients who do not show them.

This reaction appears to be of little aid clinically, and is too inconstant to be of any practical importance.

PRESENT RECOMMENDATIONS IN THE USE OF THE ANTIGEN OF STREPTOCOCCUS CARDIOARTHRITIDIS

The consideration of paramount importance in employing Streptococcus cardioarthritidis soluble antigen for therapeutic purposes is that of so regulating the individual doses that no noteworthy reactions follow them. This means that best results are to be obtained with very small doses. The fact that overdosage delays the onset of reactions must always be borne in mind because with such doses administered at the four-day intervals recommended their cumulative effects may amount to nothing more than a general activation of the disease in which the reactions to individual doses are entirely obscured. Since the objective and subjective symptoms constituting the general and focal reactions to this antigen are identical with those exhibited in a spontaneously arising exacerbation of the disease, it is only natural when the delayed symptoms from overdosage appear, to regard them as a natural exacerbation of the disease unassociated with the treatment. If this is done, however, it practically always means failure in this form of treatment. From a practical standpoint, the best results will be obtained for the patient *if all such activations of symptoms are ascribed to overdosage of antigen and further reduction of dosage practiced accordingly.* Our experience has been that if reactions of all sorts can be avoided,

the patients do remarkably well. We therefore recommend beginning with 0.05 c.c. of the 1:1000 million dilution injected intradermally. This initial dose depending on the patient's degree of hypersensitiveness, will excite within the first forty-eight hours, rarely, the primary type of reaction; frequently, a period of euphoria; or, quite commonly, the secondary type of reaction. In the first instance, the dose is very much too large; in the second, it is much too large; and in the third, while still too large, it is approaching the proper amount. In the first instance, reduce dosage to one-hundredth of the initial amount; in the second instance, to one-tenth the original dose; and in the latter case, continue the dosage constant upon repeated subcutaneous injections every four days. The secondary type of reaction will come on earlier, be milder and of shorter duration with each repetition until no reaction whatever can be detected. The dosage now may be regarded as properly adjusted for the particular patient. After reactions fail to appear following the injection of the dosage as adjusted, additions of 25 per cent to 50 per cent increments may be made from time to time. If any increased dosage elicits a reaction, this is the signal for repetition of dosage without further increase until a reaction fails to follow the injection.

In this plan it is more important to avoid reactions than to try to build up the dosage. Dosages without perceptible reactions following them appear to build tolerance but excessive dosage appears to hinder all semblance of the building of tolerance. The usual finding is that one will have to repeat the dosage which elicits a prompt general reaction from three to eight times before any additions to it may be practiced with benefit. It thus appears that patients will continue with the 1:1000 million dilution for a month or more before the dosage is built up to such volume that it is more conveniently administered by employing the 1:100 million dilution. This latter being ten times the strength of the former dilution furnishes equivalent doses in one-tenth of the volume attained with the former dilution.

In this manner tolerance may be built up slowly so that in certain individuals with long standing chronic arthritis one may after three months or more, pass to the 1:10 million dilution, or finally to the 1:1 million dilution. These latter dilutions are employed much less frequently in practice than the first two because in the less obstinate cases complete quiescence of the disease may be obtained with 1:1000 million alone, or when it is supplemented by the 1:100 million dilution. The benefits gained may or may not be permanent. Relapses occur frequently, so that two recommendations further are made.

1. In patients with rheumatic fever, antigen is not used except as a follow-up treatment after the antiserum. The course is begun after the period of serum disease has passed, namely, twelve to seventeen days after the initial injection of the antiserum. After carrying the patient up to 0.5 c.c. of 1:100 million dilution the course is discontinued after repeating this dosage three times. The patient is then advised to take each spring and fall, for several years, a short course of antigen just prior to the season of greatest prevalence of rheumatic fever. These courses are begun with 0.05 c.c. of 1:1000 million dilu-

tion and built up to a tolerance of twenty to fifty times this amount. This can usually be done in six to twelve injections.

2. In chronic arthritis after the initial course of active treatment with injections every four days has eliminated the signs of active inflammation in joints, the intervals are prolonged to seven, ten, fourteen, twenty-one, and finally to twenty-eight days. A dosage of about one-tenth to one-twentieth of that attained in the more active course of treatment is now administered every month for a year or more. This plan appears to be effective in maintaining the improvement gained and in preventing relapses.

The following selected protocols illustrate certain features of the technic in the therapeutic application of the soluble antigen of Streptococcus cardioarthritidis in cases of chronic arthritis:

CASE 3.—S. S. White, female, aged twenty years, typist. Diagnosis: atrophic arthritis.

This patient when first seen on March 4, 1929, was suffering from a multiple arthritis of the atrophic type affecting particularly the small joints of the hands, the wrists, the right elbow, and right knee. She had diphtheria and measles as a child and also tonsillitis occasionally. At the age of twelve years she had a painful swollen ankle which returned to normal after a few days. At the age of fourteen years she developed a tenosynovitis with puffy swellings on the backs of both hands, which persisted without any particular inconvenience. Three years ago at the age of seventeen years, she developed swelling, redness, and pain about the middle joints of the fingers and gradually similar involvements of the wrists, elbows, and knees appeared. The tonsils were removed in 1927, or one year after the onset of the arthritis in the small joints of the hands. Five months before coming to the office she went under the care of a very careful internist who placed her in a hospital for extensive diagnostic studies. No definite focus of infection was found. At the time of the examination she was in great discomfort because of multiple swollen, tender and painful joints of which both wrists, the metatarsolphalangeal joints, the phalangeal joints and right ankle were the most active. The fingers presented the typical fusiform appearance. The interosseus muscles of the hands were greatly atrophied, and the puffy swellings of tenosynovitis appeared on the backs of both hands. She weighed 85½ pounds; was 61 inches tall and showed a regular pulse of 84 per minute. The temperature was 99.2° F. and the blood pressure 120 mm. mercury, systolic and 68 mm. diastolic. Careful examination revealed a subacute pharyngitis; slight impairment as of thickened pleura over the lower right chest posteriorly and a soft systolic murmur at the cardiac apex which was not transmitted outward. The laboratory findings were:

Blood count: Hemoglobin 90 per cent.
Erythrocytes 4,880,000.
Leucocytes 10,000.
Differential: Polymorphonuclears 53 per cent; lymphocytes 43 per cent.
Blood urea nitrogen 13 mg. per 100 c.c. blood.
Blood uric acid 3.8 mg. per 100 c.c. blood.

Opsonic index of the blood serum against Streptococcus cardioarthritidis was 1.2 and it agglutinated suspensions of Streptococcus cardioarthritidis up to dilutions of 1:640.

Immediately prior to coming under treatment, from January 13, to February 23, 1929, she had received six injections of Streptococcus cardioarthritidis soluble antigen. The 1:10 million dilution was employed subcutaneously at weekly intervals in increasing dosages from 0.05 c.c. to 0.5 c.c. The reactions with pain, swelling and redness about the joints were so severe following these treatments that she discontinued them. From her account of the symptoms following the injection of 0.5 c.c. of 1:10 million dilution of Streptococcus cardioarthritidis soluble antigen on February 23 it was evident that she had had both the primary and the secondary phases of the general reaction and consequently her treatment was started

on March 7 with one one-hundredth of the dosage last received, namely, 0.05 c.c. of the 1:100 million dilution. Upon studying her reactions to this amount it was still regarded as too large and was reduced to 0.03 c.c. and later to 0.02 c.c. The following represent the amounts used in the first twelve treatments at weekly intervals and serves to illustrate the process of adjusting dosage to the individual case: 0.05, 0.05, 0.03, 0.03, 0.02, 0.02, 0.03, 0.03, 0.05, 0.07, 0.07, 0.1 c.c. These treatments covered the period from March 7 to May 24, inclusive. From May 24, to July 12 inclusive, weekly injections of 0.1 c.c. were used, and thereafter until April 17, 1930 an injection every two weeks was practiced—the amounts used per dose were 0.05 c.c. to 0.1 c.c. of the 1:100 million dilution. From April 27, 1930 to date the amount has been continued at 0.1 c.c. of the 1:100 million dilution per injection but the treatments have been spaced at intervals of three weeks.

No foci were removed in this patient, and no medicine administered. Following the fourth injection in the course, the patient returned to her work as a typist and has continued uninterruptedly since. She has remained free from subjective symptoms and objectively no signs remain about any of the joints, except that from time to time a very slight puffiness from the tenosynovitis is noted over the backs of the hands. This case is presented to illustrate:

The aggravation of symptoms under the larger dosage of the antigen; the improvement beginning promptly under much smaller dosage; the schedule of dosage as used early in the course in adjusting it to the patient's tolerance; and the plan of maintaining a small dose at lengthened intervals in treatment over a prolonged period after the arthritis has become quiescent.

CASE 4.—J. R. White, male, aged fifty-four, printer. Diagnosis: atrophic arthritis with deformities.

This patient was seen first in October, 1929. He had suffered from a multiple arthritis for the past thirteen years, and presented the ulnar deviation of the fingers of both hands so characteristic of arthritis deformans. His father, two brothers, and a sister had died of pulmonary tuberculosis. The patient had had in childhood, measles, chickenpox, pertussis, and mumps. He could recall no other illness except that he has been particularly susceptible to "colds in the head." For several weeks prior to the onset of the arthritis, which began in the joints of the fingers, he presented an irregular temperature which was diagnosed by his physician as "intermittent fever." He has never suffered greatly from pain in conjunction with the swollen, stiffened joints. The ulnar deviation of the fingers has been noted for seven or eight years. There has been very gradual progress of his joint involvements, so that during the years since the onset he thinks that it has at one time or another involved "practically every joint in the body." He has been able to continue his work as a printer but for the past four or five years has been greatly handicapped because of stiffness and deformity of the hands.

Upon physical examination the outstanding features were the multiple distorted and deformed joints, the undernutrition, the atrophy of the skeletal muscles, and considerable disability because of moderate contractures of the wrists and elbows, and marked limitation in the movements of the fingers, wrists, elbows, shoulders, knees, ankles, and toes. The patient was sixty-eight inches tall and weighed one hundred forty-three pounds. The temperature was 98.6° F.; the pulse regular at eighty-one beats per minute; and the blood pressure was 136 mm. of mercury, systolic and 84 mm. diastolic. The left tympanum showed a perforation but no inflammation. The inferior turbinates were large and the mucous membranes of the nose and pharynx were hyperemic. An excess of clear mucus appeared on the posterior pharyngeal wall. The frontal and maxillary sinuses were clear. The tonsils were small and without gross evidence of infection. Many of the teeth had been extracted. The remaining ones showed no evidence of apical infection upon transillumination nor by x-ray examination. The findings over the pulmonary and cardiac areas and over the gall bladder and appendix did not reveal anything of note. There was a slight distension of the bursae about the knees and considerable of those about the ankles. A pitting edema of both legs extended upward over the lower third of the tibiae.

The laboratory findings were: Hemoglobin 80 per cent; erythrocytes 4,140,000 and leucocytes 5,000 per c.mm.; polymorphonuclears 68 per cent; lymphocytes 26 per cent; mononuclears 2 per cent; eosinophiles 4 per cent. Blood urea nitrogen 11 mg.; blood sugar 100 mg.; and blood uric acid 3.4 mg. per 100 c.c. blood. Throat culture negative for Streptococcus cardioarthritidis. Opsonic idnex for Streptococcus cardioarthritidis was 0.8. Sedimentation of erythrocytes was 16 mm. in one hour. Urine: clear yellow, acid, specific gravity 1.020; no sugar; no albumin; no casts; no pus cells.

This patient was treated with the antigen of Streptococcus cardioarthritidis (Table III).

TABLE III

			BODY WEIGHT POUNDS
10/18/29	0.1 c.c. of 1:1000 million	dilution, intradermally	142¾
10/25/29	0.2 c.c. of 1:1000 million	dilution, subcutaneously	142½
11/ 1/29	0.05 c.c. of 1:100 million	dilution, subcutaneously	143¼
11/ 7/29	0.25 c.c. of 1:100 million	dilution, subcutaneously	143½
11/14/29	0.1 c.c. of 1:10 million	dilution, subcutaneously	144
11/21/29	0.06 c.c. of 1:1 million	dilution, subcutaneously	144½
11/29/29	0.3 c.c. of 1:1 million	dilution, subcutaneously	144
12/ 7/29	0.03 c.c. of 1:10 thousand	dilution, subcutaneously	144¾
12/14/29	0.15 c.c. of 1:10 thousand	dilution, subcutaneously	144¾
12/21/29	0.15 c.c. of 1:10 thousand	dilution, subcutaneously	143½
12/28/29	0.2 c.c. of 1:1 million	dilution, subcutaneously	145¾
1/ 4/30	0.4 c.c. of 1:10 million	dilution, subcutaneously	145¾
1/11/30	0.08 c.c. of 1:10 million	dilution, subcutaneously	144¾
1/18/30	0.15 c.c. of 1:10 million	dilution, subcutaneously	146¾
1/25/30	0.3 c.c. of 1:100 million	dilution, subcutaneously	144
2/ 1/30	0.1 c.c. of 1:100 million	dilution, intravenously	144½
2/15/30	0.1 c.c. of 1:100 million	dilution, intravenously	145¼
3/1 /30	0.2 c.c. of 1:1000 million	dilution, intravenously	144¼
3/15/30	0.2 c.c. of 1:1000 million	dilution, intravenously	145¾
4/ 5/30	0.2 c.c. of 1:1000 million	dilution, intravenously	147
4/26/30	0.2 c.c. of 1:1000 million	dilution, intravenously	147½
5/17/30	0.2 c.c. of 1:1000 million	dilution, intravenously	148

This patient exemplifies the low grade indolent type of chronic arthritis which grew worse slowly but very persistently in spite of a great variety of measures used in its treatment.

The complete protocol of the injections is presented to show the rapid increase of dosage, in contrast with the case presented above, and to emphasize particularly that dosage must in all cases be adjusted to the individual patient. In this case moderate focal reactions were elicited with the rapidly increasing doses, but general reactions were not noted even though the dosage was carried up to 0.15 c.c. of a special dilution of 1:10,000. Thereafter it was gradually reduced in an effort to find that amount which appeared best suited to this case. After some weeks a basic amount of 0.2 c.c. of the 1:1000 million dilution administered every two weeks was established.

The improvement in this patient was unmistakably noticeable following the fifth injection, and has continued steadily since. He has gained steadily in strength so that he can go through his day's work without experiencing the inordinate fatigue formerly so troublesome. The arms which could scarcely be raised to the horizontal position now are readily raised above the head and the patient experiences the great pleasure of buttoning his collar in the back, combing his hair, and scratching the back of his neck. The edema of the legs, and the distension of the bursa about the ankles have disappeared. The patient is bright and cheerful instead of haggard and morose. By means of special exercises he is cheerfully cooperating in attempts to overcome the contractures of the wrists and the deformities of the hands. Progress in this is being made but much remains yet to be accomplished.

SUMMARY

A special technic is necessary in the use of the antiserum of Streptococcus cardioarthritidis in the treatment of rheumatic fever in order to avoid the undesirable "focal reaction" following serum administration. This technic is presented in detail.

The possibilities of an aqueous extract of Streptococcus cardioarthritidis in the treatment of rheumatic fever, as well as chronic atrophic and hypertrophic arthritis are discussed. In its use the importance of regulating dosage so as to avoid focal and general reactions is emphasized. The present development of the author's technic and its application is recorded.

These products and the methods of their therapeutic application are to be regarded as in the developmental stages, so that further modifications are to be expected.

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N. E. CORNER THIRTY-SIXTH AND WALNUT STREETS.

THE ALLERGIC JOINT*

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GENERALLY speaking, there are two types of arthritis which are identified in various ways. The type of arthritis variously known as hypertrophic, degenerative, or ostearthritis, is recognized almost universally as a noninfectious, combined osseous and chondral degeneration appearing after the fifth decade of life, accompanying similar changes in all of the other body tissues. The characteristic findings of this type of degenerative arthritis are readily recognized, and the pathologic picture is well understood.

The second type of arthritis which is classified by various writers as atrophic, proliferative, infectious, or rheumatoid arthritis, encompasses a great number of dissimilar joint lesions with only a single characteristic sign, inflammation. Under these headings are found multiple, progressive joint involvement, persistent inflammation localized in a single joint, and fleeting joint lesions which heal spontaneously. Obviously, some differentiation must be made on a clinical and etiologic basis between these varied subtypes of this group of arthritides, before a therapeutic régime can be developed.

In this paper we will endeavor to show that in addition to the recognized specific arthritic lesions such as the tuberculous, the gonococcal, and other frankly infectious arthritides, there is another type which may be identified by constant signs, both clinical and pathologic. Not only may this type be recognized, but, further, the therapy is the same in all cases. We realize that the term allergy has been used loosely in many instances in the literature, nevertheless we have found no better descriptive term than the allergic joint for the type of disease which we shall describe.

One of the authors (Freiberg)[1] has noted the development of a characteristic joint lesion in rabbits following the repeated injection of a bacterial filtrate. The joint changes which followed the repeated injections of this bacterial filtrate were localized, altered tissue responses, otherwise identified as a hypersensitivity reaction to the products of bacterial growth. It is this disease process which is termed allergy. Following the repeated intraarticular injection of a bacterial filtrate, in the rabbit, a monarticular arthritis developed. This arthritis did not become evident until two or more injections of the filtrate had been made. With each successive injection the localized reaction in the joint became more pronounced. Coincidentally, in the rabbits which had received these bacterial filtrate injections, there developed not only specific agglutinins in the blood, as shown by a high titer serum agglutination reaction against the bacterium used in making the filtrate, but also a skin hypersensitivity to the filtrate when injected intradermally. Other factors possibly concerned in these reactions, such as nonspecific foreign proteins and variations in

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hydrogen-ion concentrations, were controlled by numerous experiments and excluded thereby.

The arthritic lesions which were produced by the injection of bacterial extracts showed characteristic changes, both clinically and microscopically. The macroscopic changes consisted in a mild periarticular infiltration, a pronounced intraarticular effusion, and a negligible loss in joint mobility or function. In the instances in which the lesion was of several weeks' duration, there was noted a well-marked atrophy of the muscles controlling the motion of the involved joint. The microscopic changes consisted in an extensive hypertrophy and hyperplasia of the synovial membrane with areas of focal collections of lymphocytic infiltration of the synovial membrane and of the subsynovial tissues. The articular cartilage had numerous small areas of necrosis with the formation of an overlying pannus of connective tissue. When new bone formation occurred, this was found at the site of ligamentous attachments, external to the joint surfaces, and in no manner interfered with joint function. A number of these experimentally produced arthritic lesions were observed over a long period of time following the injections of the bacterial filtrate, and though the periarticular infiltration disappeared entirely within several weeks, after several months had elapsed the synovial membrane hyperplasia and the muscular atrophy still persisted. It was interesting to note that the latter changes existed long after the joint effusions had entirely vanished. In fact, in several instances nine months after the last injection of the antigen, the synovial membrane was appreciably thicker than normal, and the knee joints showed a characteristic relaxation.

Of the many types of human arthritis, excluding the specific arthritides, such as the tuberculous, the gonococcal and the septic forms, differentiation into definite groups is always most difficult if the disease is of many years' standing. When an arthritic lesion is progressive in nature, even though it be confined to a single joint, so many changes occur due to the efforts of nature to accommodate the joint to the irritating lesion, that the lesion itself may be almost completely masked. Extensive deformities caused by prolonged overaction of the stronger muscle-groups resulting in actual dislocations and acute contractures of the soft tissues, not infrequently stimulate the formation of new bone in an attempt to limit the pain. Under these conditions, the etiologic factor may be suggested, not by the clinical picture, but by the bacteriologic reactions. From a clinical point of view this group of arthritides is of less importance, because the damage to joint function already has occurred. Our interest has been centered chiefly on the less advanced cases, those in which one or many joints are involved, but few severe deformities have developed. At the present time we are often unable to conclude from a study of cases of the former type what the clinical manifestations of the disease were at the onset, and whether the various types of therapy instituted previously have altered the characteristics of the clinical picture. It is for this reason that we shall confine the discussion in this paper to a group of cases, all similar in many respects, and all reacting in a like manner to the bacteriologic tests and treatment.

The type of arthritis which is designated as allergic has a definite group of clinical findings. The joint, whether it be a knee or a finger, appears fusiform,

has slight or no periarticular infiltration as determined by palpation, shows moderate limitation in function, is distended with fluid, and has a characteristic boggy feel on palpation. Roentgen films show some soft tissue thickening, moderate irregularity, and narrowing of the joint surfaces, but no extensive newbone formation. The history of the lesions frequently goes back many years, and it is also a frequent finding that at irregular intervals normal joints have become involved and have remained enlarged. It is a surprising fact that in the majority of these cases, although pain is present, it is rarely severe, and is not the chief factor in causing the patient to seek treatment. It is the unsightly appearance of the joints, and the limitation of activity which have influenced the individual to seek relief. Aspiration of the joints has been of no diagnostic or therapeutic aid in this group of cases, excepting to exclude the various specific arthritides. The fluid obtained on joint aspiration has in each instance been an effusion, yellow in color, clear or very slightly cloudy, and negative on culture. In a series of approximately one hundred cases of nonspecific arthritis, slightly more than 30 per cent have been classified as allergic. This statement is based not only on the clinical and laboratory findings of the initial examinations, but also, and more certainly, after a period of extensive therapy. No case has been classified as allergic arthritis unless positive intradermal reactions have accompanied the injection of an autogenous vaccine, and improvement or complete cure has followed a period of treatment.

It seems necessary, at this point, to digress and briefly review a series of clinical-bacteriologic studies which have been of great importance in determining our treatment of these cases.

During the past five years one of us (D.), together with his coworkers, has been engaged in a comprehensive study of vaccine therapy in which particular attention has been paid to the selection of organisms to be used as antigens. We have been especially interested in the possible significance of intradermal tests when employed to indicate specific susceptibility to bacterial antigens. The general problem and method of approach was first described by Wherry[2] in 1927 and was further elaborated by Dorst and Wherry in 1928.[3] Subsequent studies are now in the hands of publishers and will appear in the medical literature at an early date. Several hundred patients have been carefully studied including cases of bacterial asthma, ulcerative and nonulcerative colitis, arthritis, certain skin lesions, and angioneurotic edema. These clinical studies tend, for the most part, to substantiate Wherry's original hypothesis, and we now believe that both susceptibility and sensitivity to bacterial strains may be demonstrated by intradermal reactions. Antigens so selected and given, by the desensitization method, yield excellent therapeutic results. Constantly, throughout our experimental work, two facts have been emphasized, and we have come to regard them as of paramount importance in effective vaccine therapy. The first is the specificity of the antigen, and the second the desensitization method of administration. The chaotic state which obtains today in the field of vaccine therapy is, we believe, primarily due to a failure to recognize the importance of these factors. Stock vaccines have failed because they completely disregard the factor of specificity. Autogenous vaccines have likewise often failed, first, because there seemed to be no method of determining

specificity, and secondly, because the specific organism selected by chance was usually given in massive doses similar to those used to protect noninfected individuals. Vaccine so given often resulted in the exaggeration of symptoms. These facts have contributed to the low status of vaccine therapy.

It seems advisable to point out a third fact which we have had brought home to us repeatedly; namely, that immunization of a noninfected individual against a specific organism is one problem, and the desensitization of an already sensitized individual is quite another, and cannot be accomplished by using massive doses. We may not go further into the discussion in this paper; the experimental studies on this subject are available for review; but we will state our general contention as follows: Individual susceptibility to a given bacterial species may be determined by intradermal reactions to properly prepared antigens. This fact is of great usefulness when one is working with an extremely varied flora.

It seemed essential to give the preceding survey as a background to a presentation of our clinical experiments with certain types of arthritis. While we are not ready to state that a positive intradermal test always indicates an allergic reaction between the host and the "active" antigens, this seems in many instances to be the case. We are certain that in our cases of asthma, of angioneurotic edema, and in many of our nonulcerative colitis cases we are dealing with patients whose disease is of an allergic nature, if we may accept the more comprehensive meaning of the term allergy, and that the positive intradermal reactions which we obtain are local manifestations of the allergic state. We have presented experimental evidence suggesting that a certain type of joint lesion is probably allergic in nature, and it now remains for us to show how this concept has been verified by clinical experience.

As suggested above, the group of arthritides with which we have been working have previously defied accurate classification. In certain respects they suggest infectious lesions: there is swelling, local heat, and subsequent atrophy of adjacent muscle groups; but here the similarity to known infectious arthritis of the "specific" type ceases.

If the fluid removed from such joints be carefully studied, we note many points of difference when compared with fluid from known inflammatory lesions. This fluid is thin and straw-colored, the cells present being chiefly lymphocytes or large mononuclears, and the total cell count is low. The general characteristics of such fluid suggest a transudate rather than an exudate. We have studied many such specimens bacteriologically, exposing the material to enriched media under various tensions of O and CO_2, but have not succeeded in isolating organisms. The time element has been extended to twelve days and then to fifteen days, and still our cultures have remained sterile. It has been suggested that these lesions may be due to some unusual form of streptococcus. We have failed repeatedly to recover it, but granting that this failure may be due to lack of technical skill, we are still at a loss to understand a pyogenic infection whose characteristics are so unlike any other recognized as such.

In our opinion such lesions are not due to active and maintained infections in the joints themselves, but are rather the expression of a sensitized tissue to

an antigen which remains in a persisting focus elsewhere in the body. Such a sensitization may be brought about in two ways: either from repeated exposure to soluble toxic products from a distant focus, or from transient bacteriemias, during which the joint cavities have been "seeded" with organisms which have failed to grow, due perhaps to reduced oxygen tension. Experimental sensitization may be produced in either way, but we are inclined to favor the concept of circulating sensitizing toxins. A joint so sensitized may be expected to "flare up" whenever it is reexposed to the sensitizing antigen, and in many instances a focus far removed from the involved joint may be a constant source of supply for the antigen which keeps the allergic reaction "active." When such distant foci are removed surgically we frequently accomplish a striking cure, but more often the removal of foci is either impossible or incomplete, and the patient's symptoms recur. It is with such cases that we have been chiefly concerned.

Each case is studied carefully from the standpoint of foci of infection. Cultures are made from postnasal secretions, from material obtained from sinus puncture, from suction in the ethmoid region, from infected teeth upon removal, from tonsils, and from the contents of the enteric tract. If an obvious focus presents itself it is given careful attention, but in the majority of cases we must attempt an exhaustive study of the flora of the mucous-membrane lined tracts of the body, for these form the great avenues of entrance. All the organisms obtained on various types of media and under differing gas tensions[3] are isolated in pure culture and skin tests are made with each individual strain. Sensitivity is indicated by marked redness, induration, and local heat. These reactions reach their height from twenty-four to thirty-six hours after the injection and disappear slowly. Organisms giving rise to such reactions are designated as "active strains" and are used singly or mixed, as the case may be, for the purpose of desensitizing the patient. It may be stated that organisms giving reactions in these cases of arthritis come most frequently from the upper respiratory tract and the colon. Often they are organisms usually designated as "normal flora," and a Freidlander's bacillus from an antrum or a strain of B. coli from the colon will, when injected, often give a marked skin reaction and a simultaneous focal reaction in the involved joint with an acute exacerbation of the clinical picture. This focal reaction gives added weight to our opinion concerning the allergic nature of the disease.

In desensitizing our patients the active strains are employed in a dilute suspension, and very small amounts of the antigen are given at each injection. Usually we begin with 0.5 minim, carefully measured from a tuberculin syringe. This dosage is continued for several days and then increased to 1.0 minim. Injections are given every day or every second day, and the dose is slowly increased by 0.5 minim intervals. Often, in dealing with extremely sensitive individuals, it is necessary to continue at the 1.0 or 1.5 minim dose for days before it can be increased. We try to avoid any marked local reaction, and all focal or general reactions, for we have learned to our sorrow that haste usually results in a severe focal "flare up," and it is then necessary to start again from the beginning.

CLINICAL STUDIES

CASE 1.—Mrs. H. C., thirty-three years of age, married. Onset sixteen years ago with swelling and pain in both knees. After nine months the right knee became well, and left knee improved. Excepting for a period of hospitalization in 1925, she has been up and about the entire time. She has noted crepitation in the left knee at all times. In May, 1928, the left knee became very swollen and painful. At irregular intervals she has had slight discomfort and stiffness of the fingers. Otherwise the history is negative excepting for constipation with occasional intermittent attacks of diarrhea, during which there would be traces of mucus and blood in the stool.

The first examination on October 3, 1928, showed a tall slender type of individual, weighing 123 pounds. The left knee was distended with fluid and motion was limited to an arc of 60° to 160°. There was marked crepitus in both knees noted on motion. The other joints showed no abnormal changes. X-ray films of the knees were negative. General examination revealed no static abnormalities in the feet or legs, but there was a slight fatigue posture. Aspiration of the left knee on October 10, 1928, yielded 150 c.c. of a rather turbid serous fluid with further amount of fluid remaining in the joint. This was sterile on culture.

Prior to her first visit, repeated attempts had been made in several clinics to find and remove some focus of infection. The teeth, sinuses, and throat had been carefully studied without positive findings. The one rather definite lead came in the gastroenteric history. Nevertheless cultures were made from materials obtained from postnasal pharynx, and after suction applied to the ethmoid region. Cultures were also made from the stools, and these alone gave significant findings. Four strains of organisms were isolated from the nose and throat secretions, and six from the stools. These were recovered in pure culture, harvested, and heat killed at 60° C. Intradermal tests were carried out using all nine strains, and strongly positive reactions were given by B. coli communior and B. mucosus capsulatus. These two strains were incorporated in a mixed vaccine, and treatment was started, using 0.5 minim of a dilute suspension. The vaccine was then sent to the patient's family physician with instructions regarding its administration. He, however, failed to recognize the importance of advancing the dosage very slowly, and in a period of fifteen days increased the amount from 1 to 8 minims. The result was an acute exacerbation of symptoms with effusion not only into the left knee, but also into the right knee, and when examined at this period, her symptoms were definitely more marked than when first seen.

The dosage of vaccine was reduced to 0.5 minim and then given in very small doses so that between December 20, 1928, and February 23, 1929, it had been increased only to 2 minims. When examined at this time, she showed little improvement. The following brief summary covers her progress during the next eighteen months. Throughout this time she carried on her usual routine and was at no period subjected to enforced rest.

March 21, 1929, definite improvement. Dosage 2 minims.

April 16, 1929, improvement continues, fluid markedly decreased in amount. Dosage held at 2 minims.

May 6, 1929, no pain, only slight effusion in left knee, right knee well. Vaccine dosage 2.5 minims.

June 10, 1929, improvement continues. States that she is better than she has been for many months.

October 8, 1929, no pain, practically no fluid.

January 3, 1930, new vaccine prepared from colon flora still slightly sensitive to M. capsulatus and definitely sensitive to B. coli. The new vaccine was somewhat more concentrated than the first with the result that there was a marked focal reaction with return of fluid to the left knee following the third 2 minim dose. The vaccine was diluted and the dose reduced to 1 minim.

February 4, 1930, feeling well. No fluid in either knee.

March 28, 1930, no subjective symptoms, no fluid. Vaccine 2 minims.

June 15, 1930, improvement holds, patient is taking long walks and plays golf without unfavorable results.

CASE 2.—Mr. A. F. This patient gave a history of fleeting joint symptoms during the past fifteen years. More recently he has had at least three severe attacks annually, involving feet, ankles, and occasionally the elbows and knees. Each attack has been followed by less complete recovery. Preceding each illness, the patient had some generalized disturbance accompanied by malaise. Excepting for an acute gastroenteric disturbance while in the Philippines in August, 1928, the patient could recall no illnesses. No probable foci of infection had been discovered. In January, 1929, he had acutely painful and swollen feet and swollen right knee necessitating bed rest. Under another physician's care he was placed on a purin-free diet for three months, with no relief.

Examination on April 18, 1929, showed effusion in the left knee joint, swollen and acutely tender feet, and ankles associated with marked muscle spasm in the feet and congenital pronation of the feet. X-ray films of the knees were entirely negative. X-ray films of the feet and ankles showed some narrowing of all of the tarsal and metatarsal joint spaces with decrease in normal density of the bones. Though conscious of no upper respiratory disturbance, and in spite of the absence of tonsils, the patient had an injected granular pharynx. Cultures were taken from the postnasopharynx and the stools were cultured. Antigens were prepared as outlined in Case 1. He was not sensitive to any of the colon flora, but gave marked reactions to a nonhemolytic streptococcus from the throat, and to a strain of B. Friedlander from the same source. Vaccine was prepared in the manner described above. On May 3, 1929, the left knee was greatly improved, though the feet showed no improvement. Iodides and cinchopen had been administered since April 18. Vaccine therapy was started on May 10; the patient still was confined to bed. On May 22, he was permitted limited activity with support for pronation of the feet. Improvement continued with resumption of normal activities until November 6, 1929. No dietary restrictions had been imposed. On this date the patient developed an acute upper respiratory infection with temperature of 101.6° F. associated with effusion into the left elbow and severe pain in the feet. This followed a period of two weeks without vaccine therapy. On November 14, having recovered from the acute upper respiratory infection, he was again skin tested with the vaccine, and developed a 4 cm. reaction. Vaccine therapy was resumed. Two weeks later pain had entirely subsided and the patient engaged in normal activities. Vaccine therapy was continued for three months. Following the disappearance of inflammatory reaction about the feet and ankles, the patient was given physiotherapy to restore joint mobility. At the present time, July, 1930, the patient states that he is free from pain and has engaged in all activities associated with those of an active business man since November, 1929. At no time during the preceding five years has he felt as well, nor has he had such a long period of freedom from arthritic symptoms.

The two cases outlined above serve to illustrate our method of procedure. The scope of this preliminary report does not permit a detailed presentation of a larger series of cases, but Table I gives interesting data obtained from a group of thirteen. Each of the patients included in this table has been as carefully studied as the ones described. No patient is included who has not been under treatment for more than nine months, and the average times since treatment was started is eighteen months.

As an adjunct to the vaccine therapy outlined, careful attention has been paid to any existing deformities and postural abnormalities. During the active phase of the disease nonoperative correction of deformities has been carried out by means of mechanical support and physiotherapy. Muscular atrophy and postural defects, when present, have been treated by carefully supervised exercises and the application of one of the various forms of external heat. In certain instances a period of bed rest seemed indicated. Surgical correction of deformities, when necessary, was not attempted until all evidence of activity in the lesion had disappeared.

TABLE I

CASE	DURATION	PARTS INVOLVED	FOCUS	ORGANISMS SENSITIVE	RESULT
1	3 years	Right knee and elbow	Sinus	Streptococcus hemolytic	Cured
2	18 months	Knee and sacroiliac	Sinus	Staphylococcus hemolytic	Cured
3	14 years	Both knees and spine	Sinus	Streptococcus nonhemolytic	Cured
4	9 years	Both knees	Colon	Bacillus coli, Bacillus mucosus capsulatus	Cured
5	2 years	Spine and elbow	Antrum	Bacillus coli, Streptococcus hemolyticus	No improvement
6	2 years	Both knees and ankles	Throat	Streptococcus, green coloration	Cured
7	4 years	Both ankles	Ethmoid	Streptococcus, nonhemolytic Bacillus of Friedlander	Cured
8	6 months (flu)	Right knee and right elbow	Ethmoid	Streptococcus, green coloration	Cured
9	3 years	Right knee	Colon	Streptococcus, hemolytic Bacillus coli	Marked improvement
10	6 years	Spine and both hips and shoulders	Colon	Bacillus coli, hemolytic (only)	Marked improvement
11	4 years	Knees	Colon	B. coli hemolytic	No improvement
12	5 years	Wrist, elbows and knees	Antrum and ethmoid	Staphylococcus hemolytic. Green producing streptococcus	Marked improvement
13	2 years	Right sacroiliac	Tonsils	Hemolytic streptococcus	Improvement

SUMMARY

Our conclusions may be outlined as follows:

1. We believe that we have demonstrated the experimental production of an allergic lesion in the joints of rabbits.

2. In cases of joint disease in the human being, we encountered a lesion similar to those produced in rabbits. We are not satisfied that any previous explanation of this type of joint lesion in human beings is adequate.

3. We believe that this lesion in the human being is also allergic, and that we have demonstrated the relationship between antigenic substances from distant foci and the diseased joint.

4. The success of our treatment, which consists, essentially, in desensitizing patients to autogenous antigens which give positive reactions, seems to justify this conception.

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707 RACE STREET.

A MICROPHOTOGRAPHIC STUDY OF FIVE VARIETIES OF ARTHRITIC STREPTOCOCCI

By David Thomson,* O.B.E., M.B., Ch.B.(Edin.), D.P.H.(Camb.), and Robert Thomson,† M.B., Ch.B.(Edin.), London

SEVERAL varieties of streptococci have now been incriminated as causes of chronic arthritis. Extensive researches have been carried out on this subject by Dr. Warren Crowe in England and by Drs. Burbank and Hadjopoulos in America.

These arthritic or "osteotropic" streptococci have been isolated from the blood, urine, feces and apices of bad teeth of patients suffering from chronic rheumatism. When injected into animals such as rabbits, it has been found that they produce swelling of the joints and lameness, and they can be recovered from the bones and joints of these animals.

Warren Crowe (1928) contributed an important paper on this subject in the *Annals of the Pickett-Thomson Research Laboratory* **4**: 398-408, with ten illustrative plates.

The several varieties of these "osteotropic" streptococci can be clearly differentiated by their colony appearance when cultivated on Crowe's medium for three days.

Warren Crowe has discovered at least four varieties of "osteotropic" streptococci. These are (1) Streptococcus zymogenes (Braxton Hicks) synonymous with Streptococcus gracilis (American writers) see Plate V; (2) Streptococcus B.7 (2) h. (Crowe's classification) see Plate I; (3) Streptococcus B.9 (1) a (Crowe's classification) see Plate II; (4) Streptococcus B.9 (3) a. (Crowe's classification) see Plate III.

In April, 1929, Dr. Burbank sent five strains of his arthritic streptococci to Dr. Warren Crowe for investigation. In his explanatory letter he states that "One is of blood-culture origin, from the human being; one isolated from the stool, and joints experimentally produced in rabbits with it; three were originally from human blood cultures, and afterwards isolated from rabbits after having experimentally produced low-grade joint involvement of long duration."

On investigating these five strains Warren Crowe gave the following opinion as to their identification.

Burbank strain	(1) *Streptococcus zymogenes*	(D.3 (1)	Crowe's classification)
" "	(2) *Streptococcus fecalis*	(D.1 (1) a.	" "
" "	(3) Viridans type	(B.9 (1) e. ?	" "
" "	(4) Colorless group	(A.1 (1) b.	" "
" "	(5) *Streptococcus zymogenes*	(D.3 (1)	" "

After this preliminary identification, Dr. Warren Crowe sent these Burbank strains to us for further photographic identification.

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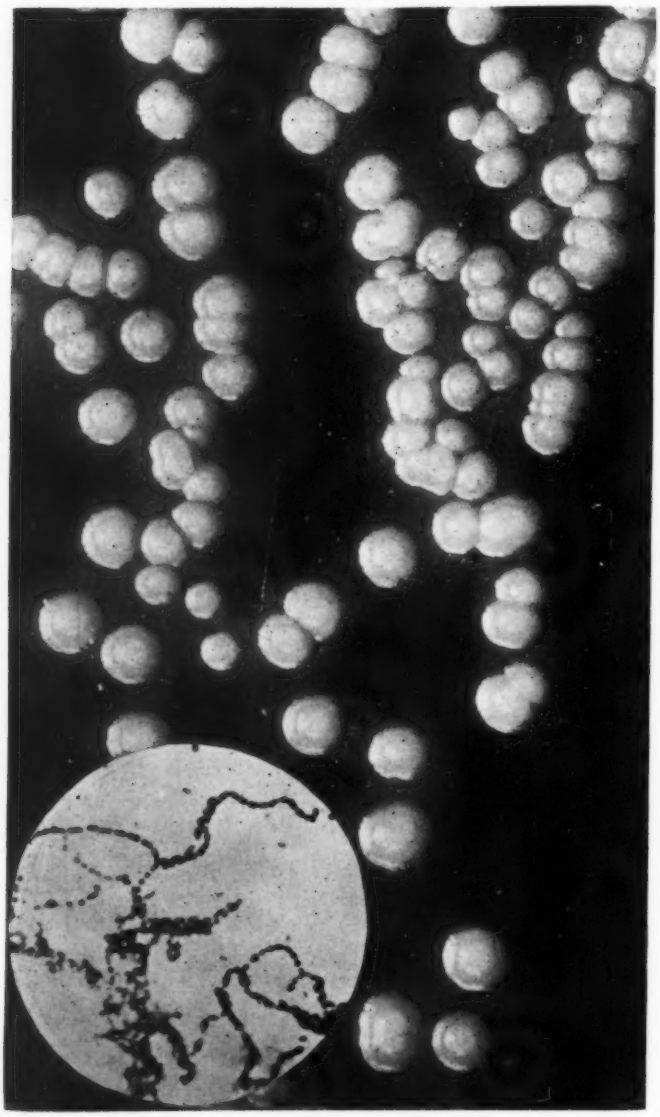

PLATE I

Burbanks Arthritic Streptococcus, No. III (originally isolated by blood culture).

Microphotograph of the colonies on Crowe's chocolate blood agar after three days aerobic incubation at 37.5°C.

Magnified 40 diameters.

The colonies are shaped like a cottage loaf. They are soft, moist and glistening with a greenish-yellow halo around them.

Iodine—(Colonies not discolored by Lugol's solution).

Inset Circle.—Represents a smear of a broth culture magnified 1700 diameters.

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite	Inulin	Salicin	Raffinose	Litmus Milk
+	+	+	+	+	−	−	+	+	+ Clot

Heat Resistance.—Negative.

This streptococcus resembles very closely Warren Crowe's "osteotropic" streptococcus B.7 (2) h; except that the latter does not ferment salicin, and does not form such long chains in broth culture.

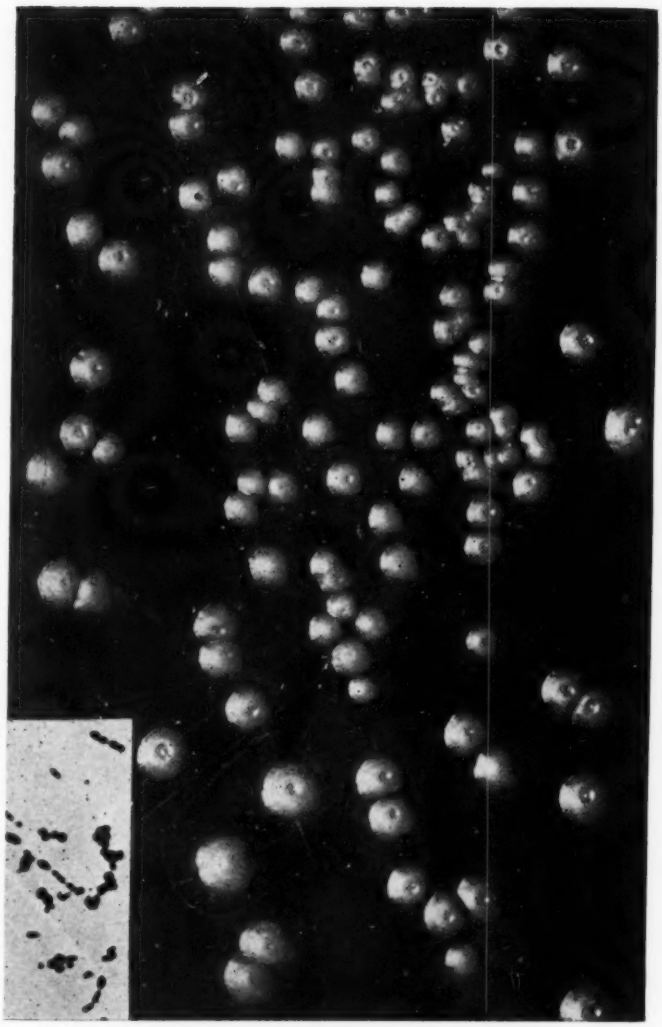

PLATE II

Warren Crowe's Arthritic Streptococcus B.9 (1) a.

Microphotograph of the colonies on Crowe's chocolate blood agar after three days aerobic incubation at 37.5°C.

Magnified 20 diameters.

This streptococcus was isolated from the apex of a tooth from a case of ostearthritis. The colonies are dry and raised and the majority of them have a central dimple. There is a narrow zone of greenish-yellow bleaching of the medium around the colonies, scarcely shown in the microphotograph.

Iodine ± (That is, the colonies are slightly browned by Lugol's solution, more especially the older colonies).

Inset.—Is a microphotograph of a Gram-stained smear of this organism ×1500.

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite	Inulin	Salicin	Raffinose	Litmus Milk
+	+	+	+	+	–	+	+	+	+ Clot in 22 hours.

Heat Resistance.—Negative.

PLATE III

Warren Crowe's Arthritic Streptococcus B.9 (3)a.

Microphotograph of the colonies on Crowe's chocolate blood agar after three days aerobic incubation at 37.5°C.

Magnified 25 diameters.

This streptococcus was isolated from the apex of a tooth and when injected into rabbits it infected not only the joints but produced hemorrhages in the tendinous portions of certain muscles, such as the biceps. It was cultured from the heart blood of the rabbit, also from the joint capsules, from the fluid of the joints, from the bone of the tibia and from the biceps.

The colonies are soft, moist and glistening, with a flattish or concave top. They are surrounded by a yellow zone of bleaching not very distinctly shown on the photograph.

Iodine ± (That is, the colonies are slightly browned by Lugol's solution).

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite	Dextrin	Inulin	Salicin	Raffinose	Litmus
+	+	+	+	–	–	–	–	–	+	–

Inset Circle.—Smear of broth culture ×1700. The broth culture shows a copious deposit with a clear supernatant fluid.

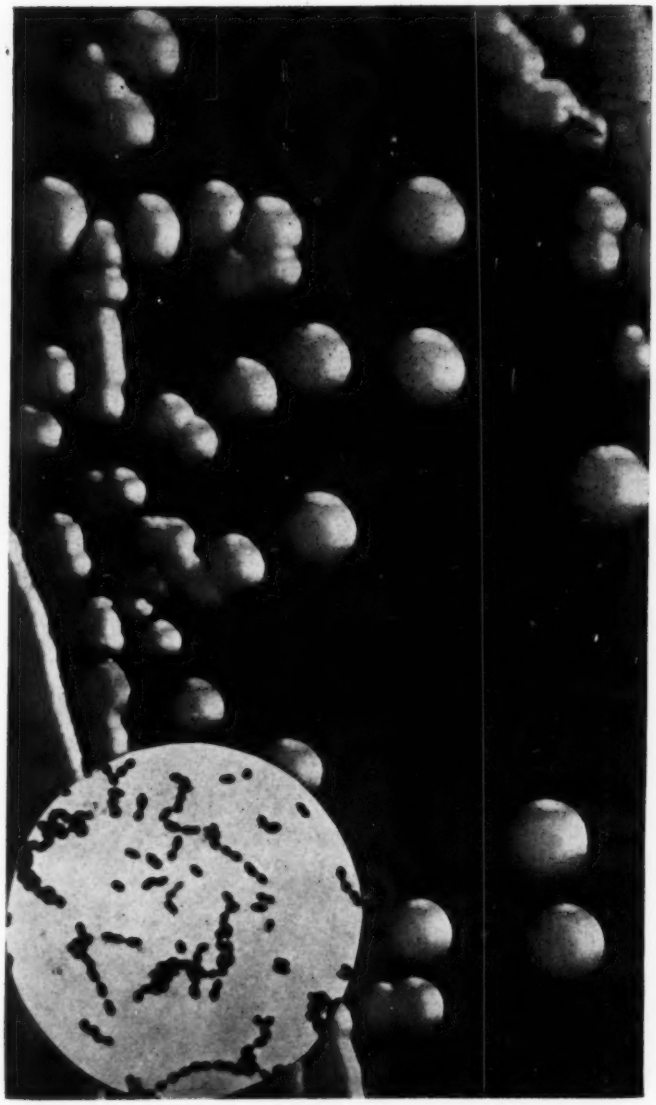

PLATE IV

Burbank's Arthritic Streptococcus No. IV

Microphotograph of the colonies on Crowe's chocolate blood agar after three days aerobic incubation at 37.5°C.

Magnified 40 diameters.

The colonies are convex, soft, moist and glistening. There is no discoloration of the medium around or under the colonies.

Iodine ++. (That is, the colonies take on a brown color with Lugol's iodine solution.)

Inset Circle.—Represents a smear of broth culture magnified 1700 diameters.

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite	Dextrin	Inulin	Salicin	Raffinose
+	+	+	+	–	–	–	–	–	+

Litmus Milk

–

Heat Resistance.—Negative.

The colonies resemble those of Streptococcus fecalis, but it differs from the latter in being nonresistant to heat. The cocci are larger than those of S. fecalis and moreover inulin is not fermented by S. fecalis.

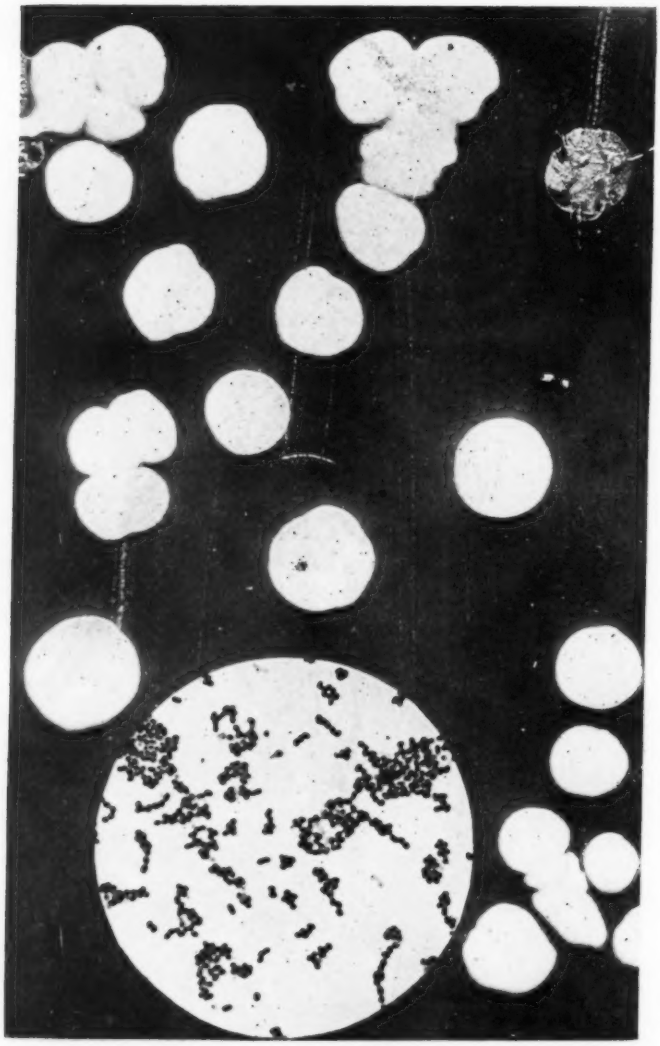

PLATE V

Streptococcus zymogenes

Microphotograph of the colonies on Crowe's chocolate blood agar after three days aerobic incubation at 37.5°C.

Magnified 20 diameters.

The colonies are porcelain white, soft, moist, glistening and they pit and blacken the medium immediately around them. The pitting and blackening is not shown on the microphotograph.

Iodine—(That is, the colonies are not discolored by Lugol's solution).

Inset Circle.—Smear of broth culture ×1700. The supernatant fluid of the broth culture is turbid.

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite	Dextrin	Inulin	Salicin	Raffinose
+	+	+	+	+	+	+	–	+	–

Litmus Milk
+ Clot

Heat resistant.

Both Warren Crowe and Burbank have found that Streptococcus zymogenes produce ostearthritis in rabbits. Crowe states that it invariably attacks the shoulder of the rabbit and produces the condition of cavitation.

This streptococcus is identical with Burbank's arthritic strains (1), (2) and (5).

NOTE.—The authors have ascertained that Streptococcus zymogenes is the same as Streptococcus gracilis of the American writers, and that it is also the same organism as Streptococcus apis (Kralx) and the Streptococcus liquefaciens of Hucker.

It is the only streptococcus known which liquefies gelatin.

The cocci are ovoid and produce only short chains in broth culture.

We found that Burbank strains (1), (2) and (5) were all Streptococcus zymogenes, since they caused blackening and pitting on Crowe's medium, see Plate V. (Crowe thought that (2) was S. fecalis, because he did not observe the pitting of the medium, which appeared later.) Burbank's strain (3), see Plate I, very closely resembles Crowe's B.7 (2) h. variety. The colonies are almost identical, the only difference is that Burbank's strain (3) ferments salicin, whereas Crowe's B.7. (2) h. does not ferment this sugar.

Burbank's strain (4) is an unusual streptococcus unknown to us. The colonies are very like those of Streptococcus fecalis, but they differ from the latter in that they are strongly iodine-positive whereas the colonies of S. fecalis are iodine negative. It also differs from S. fecalis in its sugar reactions and the cocci are very much larger than those of S. fecalis. On the other hand it does not appear to us to belong to Crowe's A.1.1. group, because the colonies are different and the cocci are too large.

We come therefore to the interesting conclusion that Warren Crowe has isolated four strains of arthritic streptococci and that Burbank has isolated three varieties.

Two of Crowe's varieties are almost identical with two of Burbank's varieties. The total of five varieties are shown on the photographic Plates I to V, and further details with regard to the fermentation reactions, etc., of these streptococci are given in the explanations of these plates.

RECENT RESEARCHES ON THE STREPTOCOCCAL ETIOLOGY OF RHEUMATIC FEVER

By David Thomson,* O.B.E., M.B., Ch.B.(Edin.), D.P.H.(Camb.), and N. Gray Hill,† M.C., M.B., B.S.(London), D.P.H.(England), London

I. PREFATORY NOTE

IN MONOGRAPH I, Vol. IV, of the *Annals of the Pickett-Thomson Research Laboratory* (1928) a complete historical account was given by Drs. D. and R. Thomson of the researches which had been carried out on the etiology of rheumatic fever up to the middle of the year 1928. At that time it appeared hopeful that the streptococcus responsible for the disease had been discovered by Birkhaug and Small in America. Another group of workers in America propounded the hypothesis that the disease was simply a state of bacterial allergy to several varieties of streptococci.

During the past two years several workers have attempted to confirm the work of Small and Birkhaug, and we have also carried out extensive investigations on the streptococcal etiology of this disease.

Lazarus-Barlow (1928), Hitchcock (1928), Nye and Seegal (1929), Lazarus-Barlow (1929) and Gray Hill (1929) were all unable to confirm the work of Small and Birkhaug since they found that the Streptococcus cardioarthritidis of Small which is identical with Birkhaug's nonmethemoglobin-forming streptococcus, was present as frequently in normal persons as in rheumatic fever cases.

Nabarro and MacDonald (1929) investigated the bacterial flora of the tonsils of children with articular rheumatism but were unable to find that this flora was any different from that of nonrheumatic children. Other workers, however, namely, Belk, Jodzis and Fendrick (1928), Flinn and others (1928), and Hart (1929) tend to confirm the work of Birkhaug and Small.

With regard to the allergy theory of rheumatic fever several confirmatory researches have appeared by Derick, Hitchcock and Swift (1929), Hart (1929), Birkhaug (1929), and Swift (1929).

II. GREEN-PRODUCING (VIRIDANS) STREPTOCOCCI IN RHEUMATIC FEVER

Leichtentritt (1929) was able to demonstrate Streptococcus viridans in the nodules in two out of seven cases of nodose rheumatism. In one of the cases the same organism was demonstrated simultaneously in the blood.

Cecil, Nicholls and Stainsby (1929) during the spring of 1928 subjected 29 patients with acute rheumatic fever to blood cultures, of whom 9, or 31 per cent, yielded a streptococcus. During the spring of 1929, 31 patients with acute rheumatic fever were studied by blood cultures, of whom 26, or 83.9 per

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cent, yielded a streptococcus. The higher percentage of positive cultures in the 1929 series appears to have been due to improved cultural methods. Of the 35 strains of streptococci recovered from blood cultures, 33 have been classified as alpha streptococci (Streptococcus viridans); one as a beta streptococcus (S. hemolyticus); and one a gamma streptococcus (S. anhemolyticus). Some of the S. viridans strains produced little green on blood mediums.

Agglutination and absorption tests indicate that the strains of S. viridans recovered from the blood of patients with rheumatic fever show a tendency to fall into specific biologic groups. In seven patients with rheumatic fever who were subjected to cultures from affected joints, 5, or 71.4 per cent, yielded S. viridans. In three patients in whom green streptococci were recovered from both the blood and joint, agglutination and absorption tests proved the identity of the strains isolated from the two sources. These observations corroborate those of previous investigators and make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection usually of the alpha, or S. viridans, type. The pathogenesis of rheumatic fever in respect to the joint lesions appears to be analogous to that of infectious arthritis and gonococcal arthritis. Bacterial allergy probably influences the clinical picture in all three conditions, but in each instance the joint manifestations are primarily dependent on localization of bacteria in the joint, with subsequent infection.

III. OTHER RESEARCHES

Gross, Loewe and Eliasoph (1929) attempted to reproduce in animals the lesions characteristic of rheumatic fever in the human being. A large number of animals representing seven species were employed. Among other materials, streptococci isolated in pure culture from the blood of rheumatic patients (proved to be so by biopsy or by autopsy), as well as the whole blood, plasma, serum, pericardial, pleural and hydrocele fluid, filtrates from tonsils, subcutaneous nodules, lymph nodes and nasopharyngeal washings obtained from such patients were used in a variety of combinations and with a number of procedures calculated to predispose the animal to the disease. They failed to reproduce the disease.

IV. RESEARCHES BY THE AUTHORS

Having failed to confirm the work of Small and Birkhaug that rheumatic fever was caused by the noncolor producing streptococcus, described by them, the authors decided to carry out further researches to ascertain if any other variety of streptococcus was persistently present in rheumatic fever children while being absent from control cases.

This investigation was carried out by a new method devised by one of us (D. Thomson) which consists in compiling extensive photographic records of cultures on Crowe's medium. This method of compiling photographic records had already been applied by D. and R. Thomson to other diseases such as influenza, scarlet fever, measles, tonsillitis, etc., and large numbers of photographs had also been accumulated of the usual flora of normal throats (see *Annals of the Pickett-Thomson Research Laboratory* **5**: 1929, and future volumes). It was hoped, therefore, that if we obtained extensive photographic

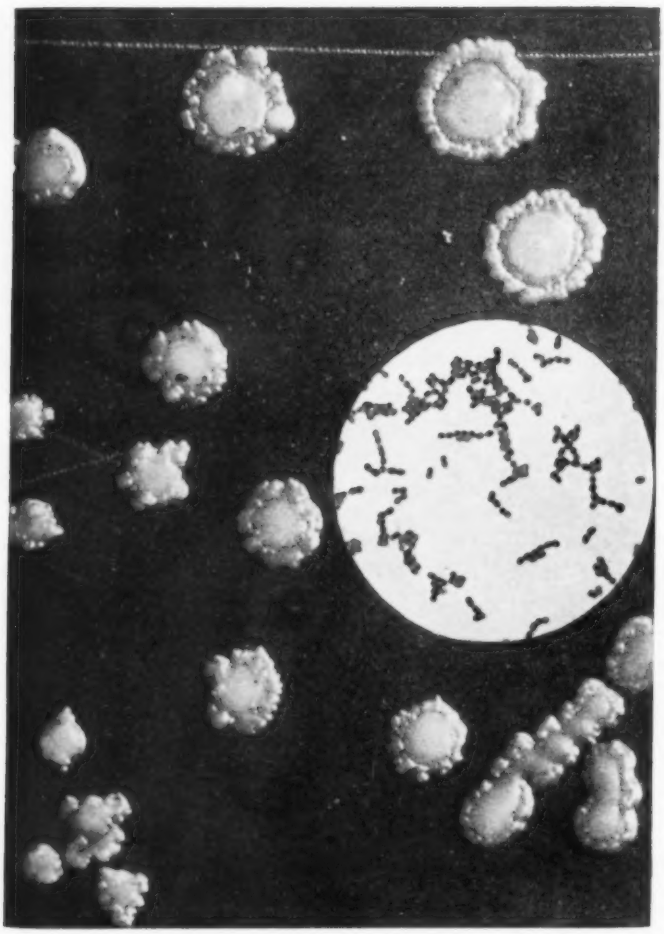

PLATE I.

Streptococcus Cardioarthritidis.—(Small, Strain R2.)

Microphotograph of colonies on Crowe's chocolate blood agar after three days aerobic incubation at 37.5°C. Magnified 40 diameters.

The colonies are greyish with a slightly greenish tinge, soft, moist and cause no discoloration of the medium around or under the colonies. The daughter colonies around the margin may not develop until incubated for several days.

Iodine.—(That is, the colonies are not discolored by Lugol's solution.)

Broth Culture.—Moderate deposit with turbid supernatant fluid.

Inset Circle.—Smear of a broth culture magnified 1700 diameters.

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite
+	+	+	+	+	–
Dextrin	Inulin	Salicin	Raffinose	Litmus Milk	
–	+	–	–	+	
				Clot	

Heat Resistance.—Negative.

NOTE.—This variety of streptococcus is believed by Small to be the cause of rheumatic fever. Small sent three of his strains R.1, R.2, and R.9 to D. Thomson and it was found that they were closely allied streptococci. Strain R.1 was Iodine +, Strains R.9 and R.2 were Iodine –.

R.2 was isolated from the faeces, R.9 and R.1 were isolated from the blood of cases of rheumatic fever. Strain R.1 did not ferment lactose and did not produce acid in litmus milk.

Compare Birkhaug's strain, Plate II.

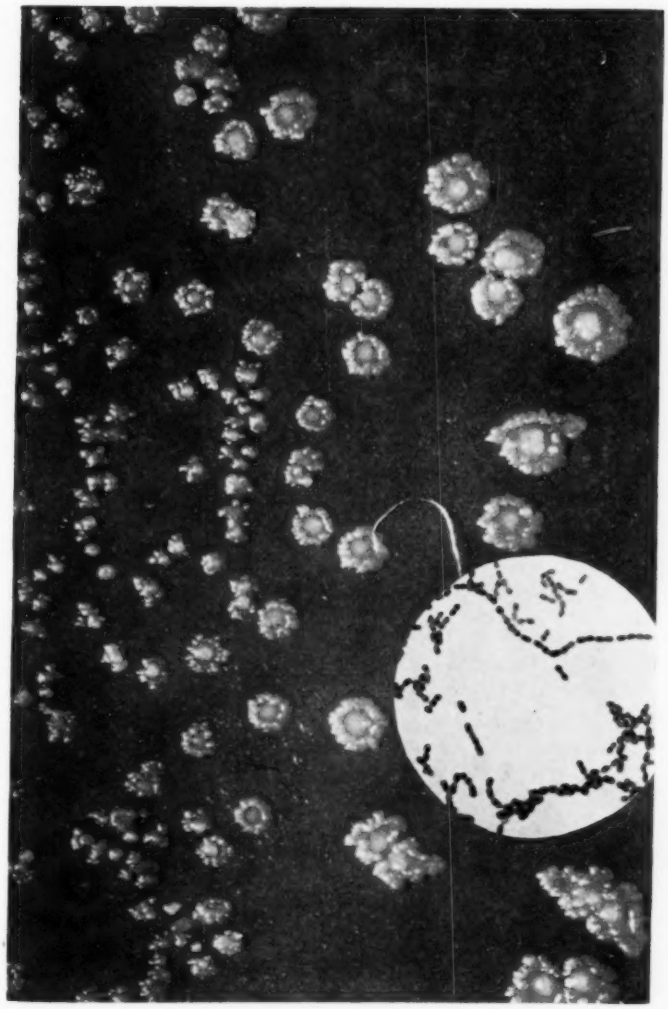

PLATE II.

Nonmethemoglobin-forming Streptococcus.—(Birkhaug. Strain R. F. 36.)

Isolated from the tonsil of a case of rheumatic fever.

Microphotographs of colonies on Crowe's chocolate blood agar after three days aerobic incubation at 37.5°C. Magnified 20 diameters.

The colonies are muddy grey in color with a tinge of green, soft, moist, glistening and very slightly adherent. There is no discoloration of the medium around or under the colonies. Iodine ++ (That is, the colonies are rendered dark brown in color with Lugol's solution).

Broth Culture.—Copious white deposit, supernatant, fairly clear.

Inset Circle.—Smear of broth culture magnified 1700 diameters.

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite
+	+	+	+	–	–
Dextrin	Inulin	Salicin	Raffinose	Litmus Milk	
–	+	+	+	+ and Clot	

Heat Resistance.—Negative.

NOTE.—This variety of streptococcus was at first believed by Birkhaug to be the cause of rheumatic fever. Several strains have been examined by D. Thomson and they have been found to be closely similar to the strains of Streptococcus Cardioarthritidis isolated by Small (see Plate I).

Birkhaug found that these streptococci produced a potent toxin which gave positive skin reactions in a large percentage of rheumatic fever cases. Birkhaug is now more inclined to believe in the allergic theory of the causation of rheumatic fever.

Further microphotographs of these streptococci of Small and Birkhaug will be found in the *Annals of the Pickett-Thomson Research Laboratory* 4: 1928, Plates 1-6.

records of cultures from the throats of rheumatic fever children, that some difference might be revealed when these were compared with similar photographs already compiled from the throats of normal cases and from various other diseases. Although the majority of the work has been confined to the bacteriologic investigation of the throat in rheumatic fever children, other material was examined when available. Thus blood cultures and cultures from postmortem material, such as the heart valves, pericardium, etc., have been investigated. The most interesting evidence which we possess, however, is that gained by the careful study of cultures from the throats of acute typical cases of rheumatic fever.

a. *Material Investigated and Technic.*—One of us (Dr. Gray Hill) having charge of one hundred beds for rheumatic fever cases, both acute and convalescent, had ample material for investigation. The culture medium consisting chiefly of plates of Crowe's chocolate blood agar was supplied by the Pickett-Thomson Research Laboratory.

1. Blood Cultures: From 10 to 20 c.c. of blood were drawn from the median basilic veins of eight cases of rheumatic fever. The technic employed was that advocated by Cecil, Nicholls and Stainsby (1928). The blood was allowed to clot and was put in the ice box overnight. The tubes were then centrifuged and the serum drawn off with a sterile pipette, care being taken to remove all the serum. The clot was then broken up and transferred to a bottle containing about 100 c.c. of testicular infusion broth.

In the majority of instances the blood cultures remained sterile. In a few cases staphylococci appeared, but in no instances was a streptococcus cultivated during life.

2. Throat Swab Cultures: Ordinary throat swabs were taken from over 34 cases of rheumatic fever children. In the majority of instances the tonsils were present and the swabs were taken from their surface. In a few instances the tonsils had been previously enucleated in which case the cultures were taken from the tonsillar fossae. Plates of Crowe's chocolate blood agar were inoculated from all tonsil swabs, and the material was rubbed well into the surface of the medium by means of a polished sterile glass shank. These plates were incubated on the average for a period of three days, and were then photographed by reflected light according to the technic developed by one of us (D. Thomson). After several photographs had been taken, these were compared with similar photographs of cultures of throat swabs from normal persons and from other types of disease such as influenza, measles, scarlet fever, ordinary tonsillitis, etc. By the careful study of these photographs it seemed to us that an unusual type of streptococcus with characteristic colonies was constantly present in the cultures from rheumatic fever throats, and this type of streptococcic colony was only occasionally present in the cultures taken from normal throats and from the throats of cases suffering from other diseases. In many instances, more especially in very acute typical cases of rheumatic fever, at least 90 per cent of the total colonies on the culture plate consisted of the unusual streptococcus. In other cases they were present only in moderate numbers but in no case did we find that they were entirely absent. They also persisted in the throat for a considerable time during the period of convalescence from the acute rheumatic fever symptoms.

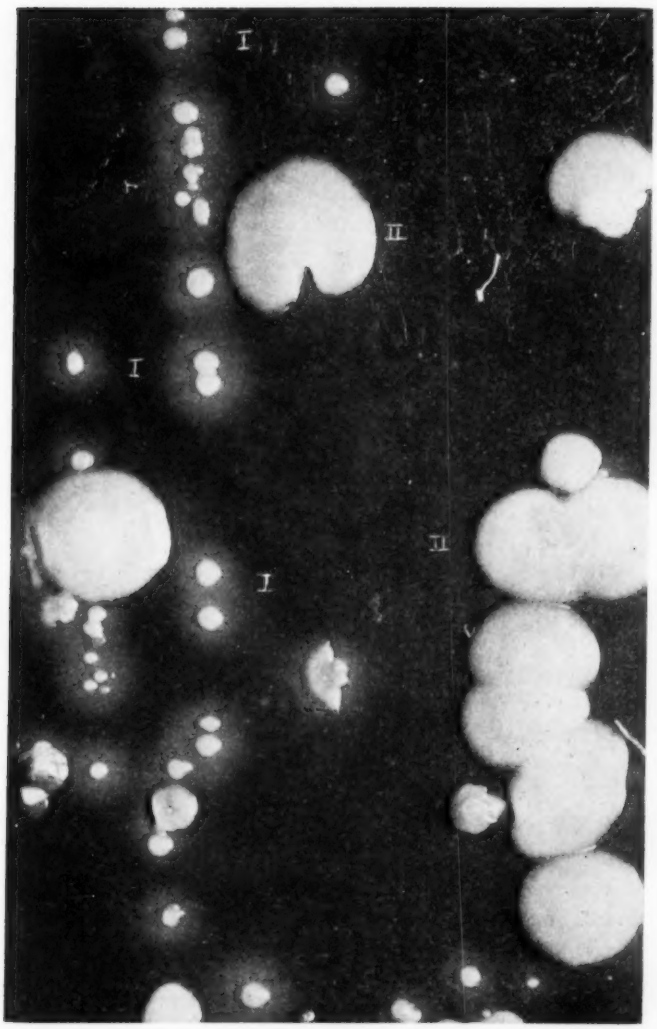

PLATE III.

Primary Culture from Rheumatic Fever Throat.—(Case Missen. This case had severe chorea.)

Microphotograph of culture on Crowe's chocolate blood agar after three days aerobic cultivation at 37.5°C. (Magnified 20 diameters.)

The predominant colonies (I) are those of a viridans type of streptococcus, which has been found by us to be present in large numbers in practically all rheumatic fever throat cultures. In very severe cases these colonies are present in very large numbers (see Plates IV and V). This type of streptococcus appears, on the other hand, to be more or less absent from the cultures made in a similar manner from normal throats and from the throats of other diseases (see Plates VII to X).

The large colonies (II) are a species of Staphylococcus albus.

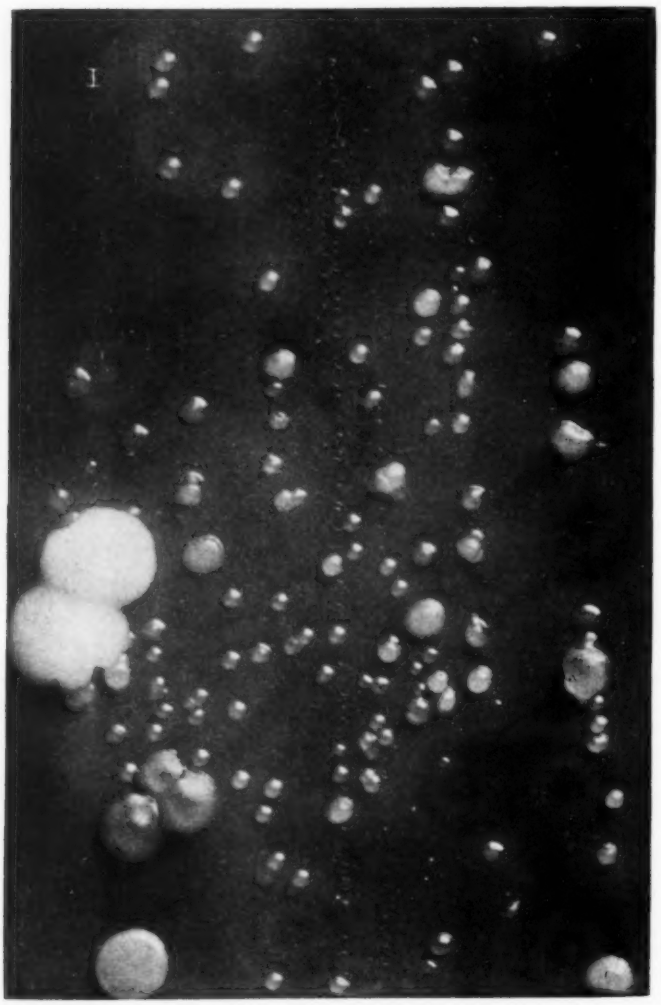

PLATE IV.

Microphotograph of Primary Culture from Rheumatic Fever Throat Swab.

Three days aerobic incubation on Crowe's chocolate blood agar at 37.5°C. (Magnified 30 diameters.)

The majority of the colonies (I) are glistening, heaped up lens-shaped and surrounded by a yellow ring of bleaching.

The colonies are Iodine + or +−.

Broth Culture.—Shows a clear supernatant fluid, with a deposit of flocculent lumps difficult to break up.

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite
+	+	+	+	+	−
Dextrin	Inulin	Salicin	Raffinose		
±	−	−	±		

NOTE.—This was an extremely severe case of rheumatic fever. Cultures from throat swabs taken at weekly intervals always showed large numbers of the heaped-up glistening colonies shown on this plate. These continued to be present for about two weeks after the acute symptoms had subsided, after which time the flora became more mixed like that of a normal throat swab.

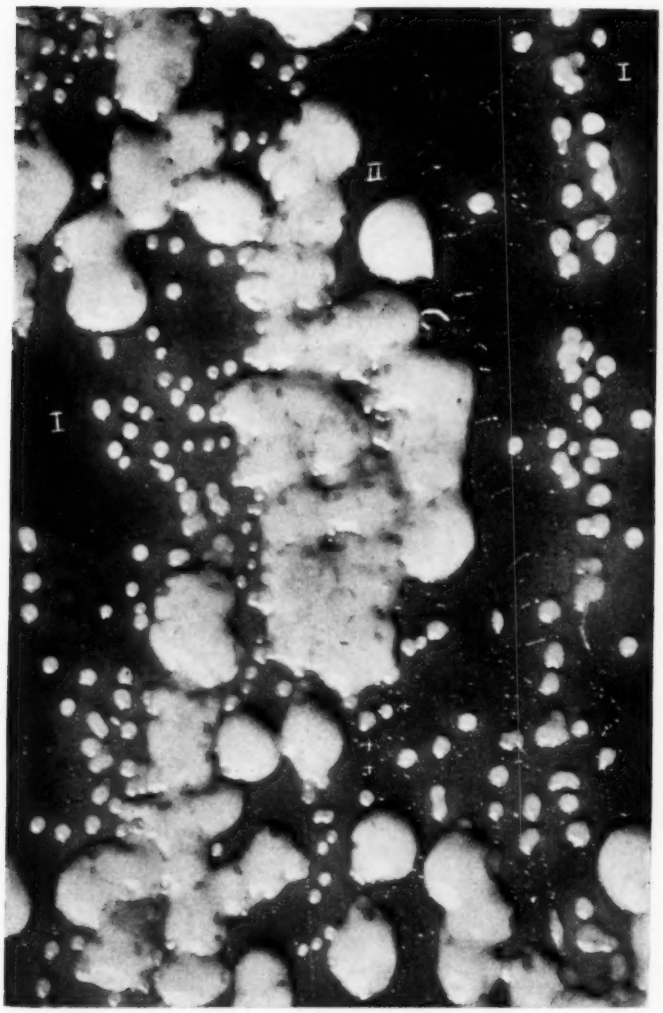

PLATE V.

Microphotograph of a Pathogen-Selective Culture from Throat of Rheumatic Fever.—(Case Campbell.) Three days aerobic cultivation of Crowe's chocolate blood agar at 37.5°C. Magnified 25 diameters.

NOTE.—The pathogen selective culturing in the patient's own blood has killed off all the throat organisms except two, namely the Streptococcus viridans with glistening lens-shaped colonies (I) and a Staphylococcus aureus (II).

Colonies (I) are Iodine +−;

Colonies (II) are Iodine −.

The colonies of the rheumatic fever streptococcus (I) were isolated in pure culture (see Plate VI for full particulars).

This was a very severe case of rheumatic fever and a large number of rheumatic nodules were present. The patient had had previous attacks and there was much cardiac damage present.

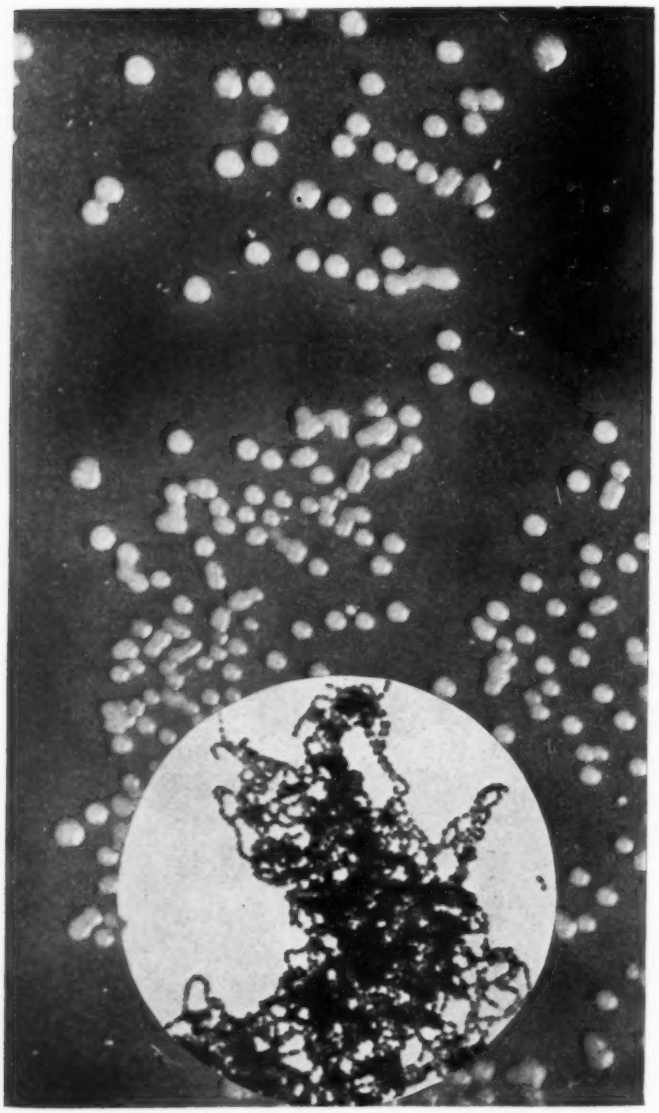

PLATE VI.

Streptococcus (Viridans Type) Isolated from the Throat of Acute Rheumatic Fever. (Case Campbell.) (Pure culture.)

Microphotograph of colonies on Crowe's chocolate blood agar after three days aerobic incubation at 37.5°C. Magnified 25 diameters.

The colonies are soft, moist, glistening, heaped up with a whitish yellow zone of bleaching around them.

Iodine +– (That is, they are changed to a light brownish color with Lugol's solution).

Broth Culture.—Shows a copious white woolly deposit with a clear supernatant fluid. Difficult to emulsify.

Inset Circle.—Broth culture, magnified 1700 diameters.

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite
+	+	+	+	+	–
Dextrin	Inulin	Salicin	Raffinose	Litmus Milk	
–	+	–	–	+	
				Clot	

The typical appearance of these streptococcal colonies characteristic of rheumatic fever is shown on Plates III, V, and VI. The colonies are as a rule somewhat spherical, smooth and glistening and are surrounded by a yellow zone of bleaching. When incubated for a period longer than three days they become more rough and opaque and tend to spread a little around their margins.

In broth cultures as a rule they produce a flocculent deposit with a clear supernatant fluid. The deposit consists of long tangled skeins of streptococci. They ferment glucose, maltose, galactose, saccharose, lactose and produce acid and clot in litmus milk. Mannite is never fermented, but occasionally dextrin.

They resemble very closely the streptococcus R.F.v. 182, isolated by Birkhaug from a rheumatic fever nodule. (See *Annals of the Pickett-Thomson Research Laboratories* **4**: 1928, Plate 4, Figs. 4-6.) They are entirely different from the S. cardioarthritidis of Small and the nonmethemoglobin-forming streptococcus of Birkhaug (see Plates I and II of this paper).

3. Pathogen Selective Cultures from the Throat: This method introduced by Cronin Lowe (1928) was adopted in two cases. The material from the throat swab was incubated with the patient's own blood for a period of twenty-four hours. Cultures from the blood were then plated on Crowe's medium and incubated for three days as usual. Plate V shows a microphotograph of a culture from a rheumatic fever throat made in this manner. Only two organisms were present, viz., Staphylococcus aureus and the typical colonies of the rheumatic fever streptococcus already described.

The second attempt at pathogen selective culturing from the throat of another rheumatic fever case was even more successful, as the characteristic colonies of the streptococcus appeared almost in pure culture.

4. Tonsil Puncture Cultures: We believed that if cultures were made from the interior of the tonsils, we would be more likely to obtain purer cultures of the streptococcus than by the surface swab method. Dr. Gray Hill tried this method following the procedure of Pearse in eleven cases.

The results were, however, somewhat disappointing. In several instances the plates were overgrown with a mass of bacteria including the usual flora of the mouth.

The streptococcus characteristic of the rheumatic fever throat swabs, except in a few instances where they were very numerous, was not nearly so much in evidence in the case of the tonsil punctures. In three instances hemolytic streptococci were obtained in the mixed flora and in one instance the Small-Birkhaug type of streptococcus (see Plates I and II were numerous).

5. Cultures from the Interior of Tonsils Enucleated During the Attack of Rheumatic Fever: Samples taken from the interior of tonsils enucleated shortly after an attack of rheumatic fever were inoculated on to Crowe's medium in the usual manner. In one of these large numbers of hemolytic streptococci were found as well as a few of the characteristic rheumatic fever streptococcus. In other cases were found hemolytic streptococci, the streptococcus of Birkhaug and Small and the characteristic viridans streptococcus.

6. Postnasal Cultures: Cultures were made from the nasopharynx in four cases, but they showed nothing unusual. The chief organisms obtained from

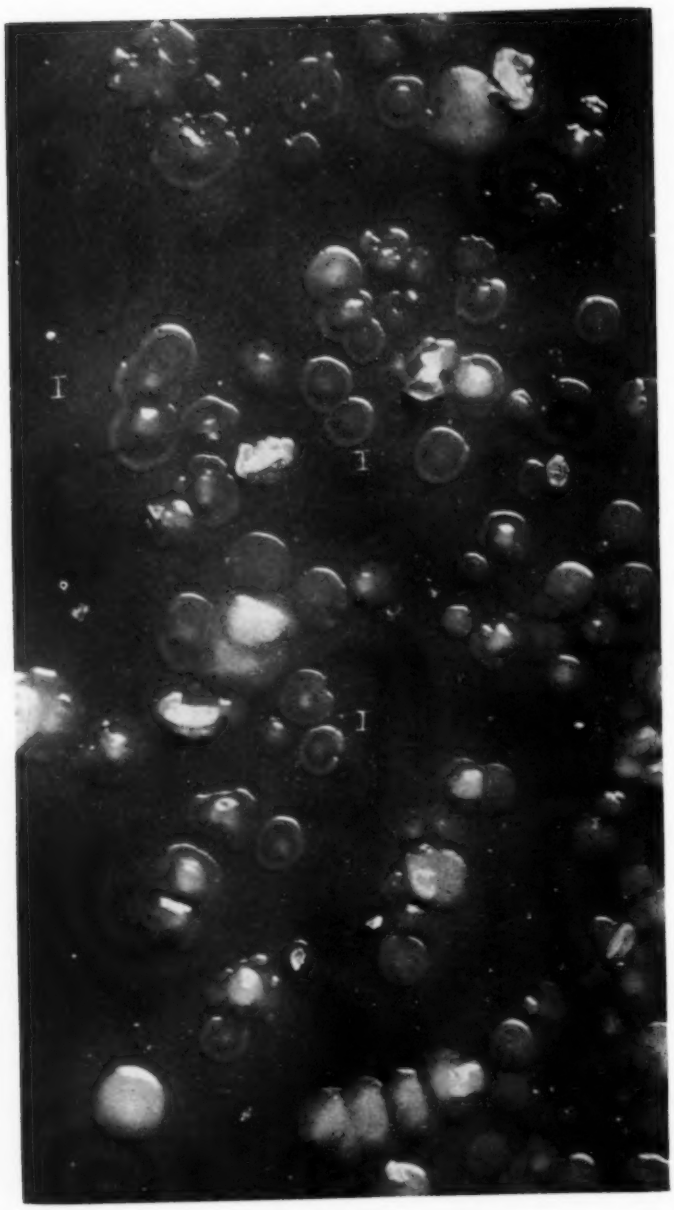

PLATE VII.

this situation were gram-negative diplococci of the catarrhalis type and streptococci of the pneumococcus type.

7. Urine Cultures: The urine in one instance was drawn off aseptically, centrifuged and the deposit inoculated on to plates of Crowe's chocolate blood agar. A Staphylococcus albus and a few diphtheroids appeared on the culture but no streptococci.

8. Postmortem Material: There is great difficulty in obtaining postmortem material from early cases of acute rheumatic fever. As a rule the cause of death is heart trouble and this usually occurs long after the acute stages of rheumatic fever have passed.

Dr. Gray Hill was able to obtain postmortem material for bacteriologic examination in three cases.

CASE "C."—Blood was taken on the third day after death. This gave a mixed growth of several organisms, among which was a hemolytic streptococcus.

CASE "S."—Cultures were taken from the mitral valve, pericardium, myocardium and heart blood, one day after death. Two varieties of streptococci were isolated from the mitral valve. One resembled somewhat the Birkhaug-Small colorless streptococcus. The other varieties produced a flat spreading growth and caused a slightly greenish discoloration of the culture medium.

CASE "M."—The pericardium was full of seropurulent fluid at the postmortem and from this pus was cultivated a Staphylococcus aureus and two varieties of streptococci. Both varieties of streptococci were of the viridans type. One produced flat spreading colonies on Crowe's medium and was long-chained. The other variety resembled the typical rheumatic fever species which we have found constantly in the throats of acute rheumatic fever cases (see Plates III to VI).

b. *Further Remarks With Regard to the Characteristic Streptococcus Found.*—If the streptococcus in question has some relation to the cause of rheumatic fever, one would expect to find it in every case, and unless we are to assume that there are healthy carriers it should be absent from practically all other throats. Streptococci giving somewhat similar colonies, however, can be found in the throats of some normal children. From our investigations it would appear that several varieties of streptococci are capable of producing this type of colony, so it is necessary to investigate this matter

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PLATE VII

Primary Culture from Measles Throat.—(Case Cooper, fourth day.)

Microphotograph of the culture on Crowe's chocolate blood agar after two days anaerobic and one day aerobic incubation at 37.5°C. Magnified 25 diameters.

It will be noted that the majority of the colonies (I) are flat and translucent with a raised margin. They are Iodine – or +–. These colonies have been found by Drs. D. and R. Thomson to be present in large numbers in all cases of measles so far examined. When isolated in pure culture, they are found to give the following sugar reactions.

SUGAR REACTIONS

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite
+	+	+	+	+	–
Dextrin	Inulin	Salicin	Raffinose	Litmus Milk	
+	+	+	+		
or –	or –	or –	or –	Clot	

This measles streptococcus resembles very closely those strains isolated from cases of measles by the American workers Tunnicliff and Ferry.

It will be noted that the type of heaped-up glistening viridans streptococcus found in the rheumatic fever cases (Plate III-VI) are conspicuously absent.

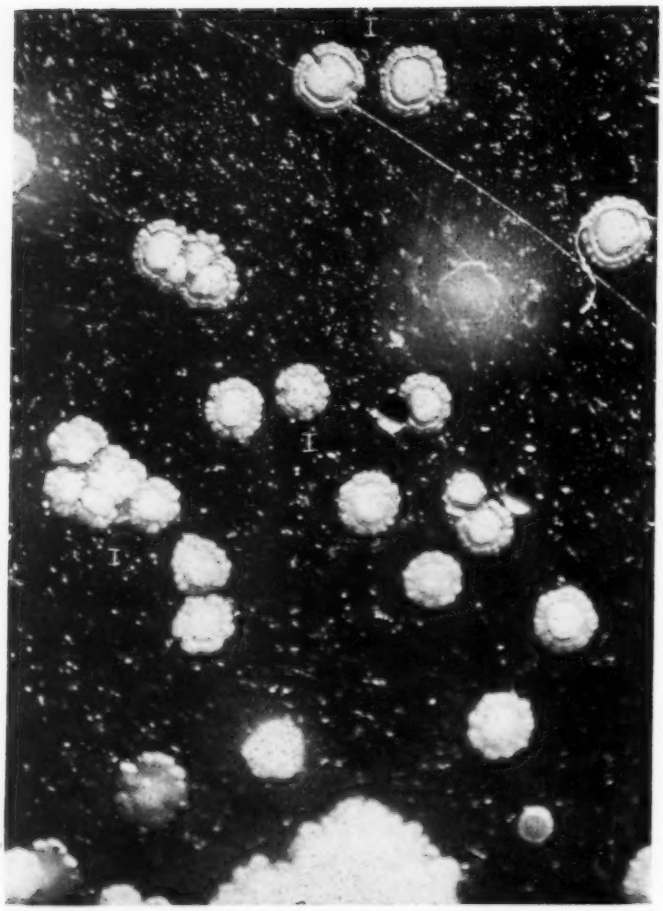

PLATE VIII.

Primary Culture from Scarlet Fever Throat.—(Case Birch, third day.)

Microphotograph of the culture on inspissated whole blood (modified Crowe's medium) after three days aerobic incubation at 37.5°C. Magnified 25 diameters.

The predominant colonies (I) are the haemolytic Streptococcus scarlatinae. These colonies are greyish, soft, moist with no color around or under them. They are Iodine—and haemolytic.

NOTE.—That the colony picture is very different from that obtained from the throat cultures of rheumatic fever, measles, etc.

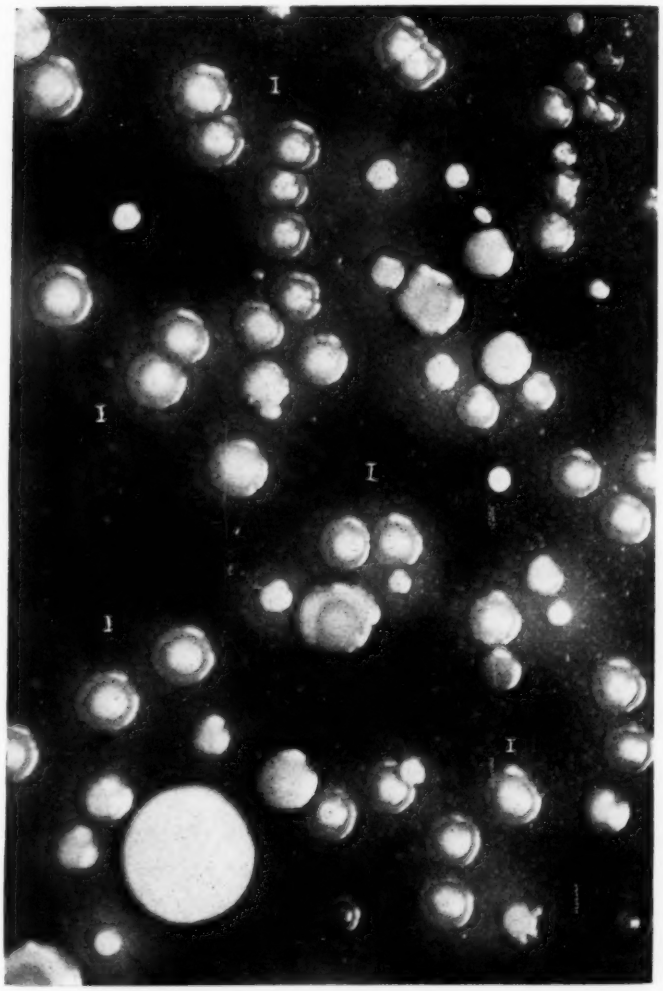

PLATE IX

Primary Culture from the Throat; Severe Influenza.—(Case Webb.)

Microphotograph of culture on Crowe's chocolate blood agar after three days aerobic incubation at 37.5°C. (Magnified 25 diameters.)

The predominant colonies (I) were whitish, soft, moist, heaped up (cottage loaf type) with a greenish-yellow discoloration of the medium around. This type of viridans streptococcus which will be noted is quite different from the types found in rheumatic fever and in measles, was present in all the cases of influenza examined, though not in such large numbers as in this very severe case.

This patient developed endocarditis with emboli and eventually died.

SUGAR REACTIONS OF THE INFLUENZA STREPTOCOCCUS (I.)

Glucose	Maltose	Galactose	Saccharose	Lactose	Mannite
+	+	+	+	+	−
Dextrin	Inulin	Salicin	Raffinose	Litmus Milk	
+	−	−	−	+	
				Slight clot	

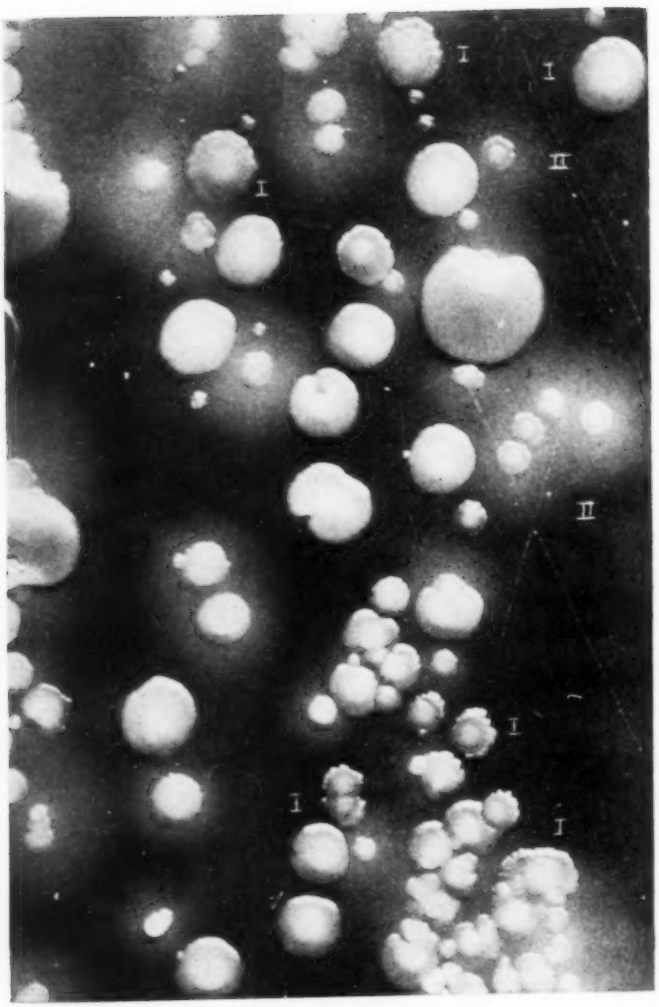

PLATE X

Primary Culture from the Healthy Throat of a Nonrheumatic Child.

Microphotograph of culture on Crowe's chocolate blood agar after three days incubation at 37.5°C. Magnified 25 diameters.

Colonies (I) which are of the Birkhaug-Small type are numerous although this child gave no history or any evidence of rheumatism. The small viridans colonies (II) appear to be of a different type from those found in rheumatic fever throats.

very carefully by employing the usual other tests for identification such as sugar reactions, skin tests, agglutination tests, etc. These tests are at present in progress but we have not yet done sufficient work to come to any definite conclusion. We wish it to be understood, therefore, that although we find this type of streptococcus constantly present in the throats of rheumatic fever patients, we do not yet claim that it has any real causal relation to the disease. Its persistent frequency, however, is sufficiently striking to compel us to regard it with strong suspicion.

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THE NUTRITIONAL FACTOR IN CHRONIC ARTHRITIS*

By A. A. Fletcher, M.B.(Tor.), Toronto

IN MOST cases of chronic arthritis, the onset appears to be initiated either by infection, by some form of trauma or strain, or by the menopause. Those associated with infection are usually cases of rheumatoid arthritis, and those with trauma and strain or the menopause, ostearthritis. But there is much doubt as to how essential and how important any of these so-called exciting factors may be as causes of the disease. In those cases which appear to be infectious microorganisms are not recovered with any certainty. When isolated, they are as a rule of low virulence and do not conform to any specific type. Most observers report that they are unable to reproduce chronic arthritis in experimental animals by the injection of these bacteria. Much uncertainty also exists as regards trauma, and the precipitating traumatism may be of a trivial nature. And while it is true that arthritis commonly develops at the time of the menopause, this change by itself could scarcely result in joint disease.

Considerations such as these lead to the belief that some state of ill health on the part of the patient has preceded the onset of the disease. This state has been vaguely designated under terms such as "constitution" or "diathesis." From a clinical standpoint it is apparent that many factors contribute to the development of this state, such as: fatigue, climate, environment, occupation, heredity, metabolism, worry, anxiety, previous disease, age, sex, diet and nutrition. This paper has to do with the nutritional and dietetic factors.

A relationship is generally recognized between the digestive system and the development and course of chronic arthritis. Some disturbance of this system, such as constipation, diarrhea or putrefaction, may precede the onset of joint disease or parallel its severity. Relief of arthritic symptoms may be brought about by changes in diet, by the use of colon irrigations, by the administration of laxatives or intestinal antiseptics, or by the implantation of acid forming organisms, and these measures calculated to correct some digestive disturbances are widely used at the present time. Goldthwaite[1] and his colleagues, Lane,[2] Rea Smith,[3] and others have directed attention to certain changes found in the abdominal viscera: visceroptosis, intestinal stasis, and bowel atony. Based on the belief that these mechanical disturbances were of fundamental importance many therapeutic measures have been carried out, which include the application of belts, postural reeducation, plastic abdominal operations, and even partial colectomy, and at times these have resulted in marked improvement of the arthritis.

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But dietotherapy in arthritis has meant many diets, some of them based upon conflicting and unscientific data. The uric acid and autointoxication theories, in particular, have resulted in undue and harmful restriction of meat and glandular foods. For many years, however, Pemberton[4] has insisted upon the value of limitation of the diet, lightening in this way the load upon both the digestive tract and upon general metabolism. He lays greatest stress upon the restriction of carbohydrate. Some years ago we observed the beneficial effects of this method of treatment, and we reported that carbohydrate restriction was most effective when vitamins were added.[5] It was suggested that in arthritis excess carbohydrate aggravates latent vitamin deficiency and to this state of malnutrition was due the susceptibility to bacterial or toxic invasion.

In a further study of the influence of high vitamin low carbohydrate diet in arthritis, special observation[6] has been made of the bowel disturbances. In the past it has been said that they were developmental or constitutional in origin or the result of some acquired defect. It is likely that many factors determine the position of the abdominal viscera and influence the tone and motility of the bowel. Our own observations indicate that they are more particularly dependent upon the nutritional state and dietetic life of the patient. In 1921, McCarrison[7] reported that he was able to produce bowel atony and mucous membrane degeneration in the colon of monkeys by feeding autoclaved diets high in carbohydrate, and it appears that the bowel changes found in patients with chronic arthritis are structurally and causally of the same nature.

These colon disturbances may be demonstrated clinically by an x-ray examination following a barium enema.[8] They include loss of tone, decrease or absence of haustral markings and increased length. The loss of tone may be most marked in, or confined to the cecum and ascending colon. At other times it may involve most of the viscus, so that with the absence of haustration the bowel presents a large sausage-shaped appearance. The atony may also result in shapelessness of the bowel, and the increased length produces redundancy and looping. Under the influence of high vitamin low carbohydrate diet, tone improves, haustral markings increase and become regular, and the colon tends to regain its normal shape and contour.

In the formation of these diets foods high in vitamin are used as far as possible and Vitamin B is given liberally in the form of wheat germ, wheat germ extract, or various forms of yeast. Wheat germ is most effective in bringing about this improvement in the colon. It may be given up to one ounce or one and one-half ounces a day. Arrangement of the diet is also essential in this treatment. Protein is supplied as meat, fish, fowl, eggs, liver, and milk, up to 50 or 60 gm. a day. Carbohydrate is reduced to 50 to 75 gm. given largely as vegetables and fruits. Fat has been allowed to make up the caloric requirement. It should be given largely as cream or butter. Some individual adjustment in diet may be necessary. There is much variation in protein tolerance, especially when putrefaction has set in. In such patients a short course of dieting with milk alone may be carried out. On the other hand, arthritic patients often show considerable anemia, and pro-

longed protein restriction is inadvisable. Patients who are overweight may, with benefit, be given diets well under the basal requirement. In those underweight, the calories should be given in the form of cream and butter to exceed a maintenance level. The changes which take place in the colon are not dependent upon bulk or roughage. Some patients do best on a bland diet; others on diet large in volume. Wheat germ may aggravate colitis if it is present, and Vitamin B is better borne as yeast or yeast extracts.

This program of dietetic treatment materially modifies the course of the arthritis and most benefit is seen in patients who show colon disturbances. Observation has been made under careful control, and diet alone in some cases may result in quiescence of the disease. There is, at the same time, improvement in the general health of the patient. The patient with arthritis is often a chronic invalid and malnutrition may be part of his physical asthenia. Increase in weight and strength, more resistance to fatigue, increased appetite, better bowel function may be part of the general improvement. In chronic arthritis a disturbance in capillary flow may be present. This, many believe, is of basic importance. (Rowntree.[9]) Many physiotherapeutic measures probably act through their influence on this system. This disturbed capillary flow may disappear under a course of dietetic treatment and the extremities cease to be damp and cold.

Treatment by diet should not be used to the exclusion of other measures. Clinical experience indicates a multiple etiology of arthritis, and treatment should embrace many measures calculated to combat the various remote and immediate causes. Some three or four hundred patients have been treated by this high vitamin low carbohydrate program, and it may be said that in many no other method of treatment has been so effective. In 60 to 65 per cent of the cases the colon showed a radiologic appearance which was considered abnormal. In these cases dietetic measures are almost always beneficial. Even in patients without abdominal disturbances treatment by diet may prove a valuable adjunct to other measures adopted.

The probable nature of the disturbed nutritional state in chronic arthritis requires some discussion. Human diets are rarely deficient in one constituent only, and it appears likely that the condition is not comparable to the specific vitamin deficiency diseases of experimental animals. McCarrison, in producing lesions of the colon by deficient and unbalanced diet, pointed out their complex etiology. He attributed these changes especially to Vitamin B deprivation, but he further emphasized the part played by lack of balance in the diet and particularly to carbohydrate excess. Deficiency of other vitamins also interferes with the normal growth of the digestive tract. Cramer[10] has shown that development of the mucous membrane of the bowel is dependent upon adequate Vitamin A. In rats fed on diets partly deficient in this vitamin, atrophic and destructive changes were seen in the intestinal mucous membrane leading to the invasion of microorganisms. The motor disturbances of the bowel are associated especially with Vitamin B deficiency, probably the thermolabile or antineuritic B_1.

The diets used in treatment involve two general principles: The liberal use of the so-called protective foods, those which are high in vitamin; and

second, the restriction of certain foods which favor deficiency disease, namely, the carbohydrates. Previous to McCarrison's observations Funk[11] had found that the ease of producing Vitamin B deficiency varied directly with the amount of carbohydrate administered, and Mellanby[12] states that the amount of cereals in the diet will determine the severity of Vitamin D deficiency disease. To replace the carbohydrate, fat may be given freely and this is in keeping with the experiments of Evans and Lepkovsky[13] who find that fat has Vitamin B sparing properties. General improvement in the diet is essential in treatment. Adequate protein of good biologic value and foods high in all vitamins, and also inorganic elements, should be supplied. Cod liver oil is often beneficial. The patient should be brought to a state of optimum nutrition.

Furthermore, the recovery period is likely to be slow. These colon changes antedate the arthritis as far as we know, and clinical histories may reveal long standing gastrointestinal disturbances in function. Faulty nutrition does its greatest harm during growth, and if this is chronic goes on to permanent structural damage: as a result, only partial convalescence may be possible. Sometimes improvement in the colon disturbance takes place in a few weeks, but more often it is a question of months. Some of these patients appear to be incapable of returning to ordinary diets. They may be permanently intolerant of carbohydrate, and it is advisable to continue more or less indefinitely these principles of dietetic treatment.

Many patients with chronic arthritis have foci of infection and the onset of the arthritis is related to active focal infection. This is true for those with colon disturbances and for those without. In patients with these colon disturbances dietetic treatment influences not only the arthritis, but also the liability to infection, and it appears likely that in these patients faulty nutrition has led to a state favorable to the development of infection. Animal experiment offers much support to this opinion. Vitamin A or B deficiency is particularly liable to be associated with infection, and in each case the deficiency disease itself may be an infectious process. Mellanby[14] would have Vitamin A the antiinfective vitamin. Variations in protein administration also influence susceptibility to infection. Of special interest in this connection is the work of Cramer.[15] He subjected rats to prolonged nonspecific vitamin underfeeding and, in these animals, avirulent organisms became pathogenic. This is comparable to the phenomenon of arthritis when organisms of low virulence bring about profound invalidism. The liability of the patient with chronic arthritis to develop focal infection is as much an expression of his chronic ill health as a cause of it, and this tendency to run chronic infections is influenced by corrective dietetic measures.

Visceroptosis and intestinal stasis, as well as atony, are associated with this state of faulty nutrition. Under a course of dietetic treatment the cecum or transverse colon may be lifted up out of the pelvis, and the splenic and hepatic flexures rise three or four inches. It is possible that visceroptosis is due to other causes, but from an examination of the x-ray plates, it is evident that the position of the bowel in the abdomen can be much modified by these diets. While prejudicial to the health of the patient, it is doubtful

whether these mechanical disturbances of the abdomen, as revealed by x-ray, represent in themselves primary causative agents in arthritis. A marked degree of stasis and atony may be seen without arthritis: as, for example, in Hirschsprung's disease. Other factors which are associated with the bowel disturbances are probably of greater etiologic importance. These are: first, general faulty nutrition leading to infectious or premature degenerative disease; and second, damage to the mucous membrane of the bowel, leading to increased permeability. In many patients the large bowel is the site of an infectious or catarrhal process evidenced clinically by colitis and by tenderness throughout the colon or in the cecal region. It seems highly probable that the diseased colon may at times be the focus of the infection or toxic agent causing the arthritis.

These colon disturbances have been observed in patients with rheumatoid arthritis and with ostearthritis, and in some with arthritis of the menopause. In all these cases dietary measures have proved beneficial. This supports the view, which is widely held, that whatever the exciting cause may be, the different forms of chronic arthritis have some causal background. Opinion is expressed that faulty nutrition is the most frequent and most important basic factor in the development of this disease, and of the various factors that go to make up the predisposing state, none is more frequent or more important than chronic faulty nutrition.

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MEDICAL ARTS BLDG.

TRAUMATIC ARTHRITIS AND THE MECHANICAL FACTORS IN HYPERTROPHIC ARTHRITIS*

By J. A. Key, M.D., St. Louis, Mo.

INTRODUCTION

CHRONIC arthritis is now recognized as probably the greatest cause of human morbidity and during recent years this disease or condition has attracted the attention of investigators throughout the world. For the most part attention has been focused upon infection as the etiologic factor in the disease. Among recent American authors Forkner and Shands,[1] Cecil,[2] Burbank,[3] and Key[4] have all obtained organisms from the blood or joints of patients with chronic arthritis and have endeavored to prove that these organisms are the cause of the disease. Unfortunately each of the above investigators has obtained one or more different organisms and no one has yet obtained acceptable proof that any organism is the cause of any of the conditions commonly called chronic arthritis; so the etiology remains obscure.

At this point it should be definitely stated that chronic arthritis is not a clinical entity, but embraces a considerable number of more or less similar conditions. These have been abundantly, but not as yet satisfactorily classified, as anyone who has studied large series of cases is aware of his own inability to fit many of the cases into any of the various classifications which are to be found in the literature. However, most of the cases fall into one of two groups: (1) atrophic, proliferative, rheumatoid, infectious, or ankylosing arthritis or arthritis deformans, and (2) hypertrophic, degenerative, senile, metabolic or ostearthritis and this is also called arthritis deformans. In this paper the terms atrophic and hypertrophic arthritis will be used. But there are, of course, many cases which do not fit into either group and other cases which appear to be a mixture of both types in one individual. Finally, after studying the subject rather intensively during the past ten years I find cases which are mixed atrophic and hypertrophic and other borderline cases which I believe are either atrophic or hypertrophic, but I am not sure which.

The pathologic picture and clinical course of atrophic arthritis resemble those of an infectious disease and for this reason the impression that some, or perhaps one of several as yet unknown organisms is the cause of the condition has been steadily gaining favor during the past few years. In hypertrophic arthritis on the other hand the pathologic picture and clinical course resemble those of a joint which is reacting to injury caused by a long continued series of insults which may be either mechanical or chemical in nature.

This paper will deal with hypertrophic arthritis and the atrophic form of the disease will not be considered. It will include a short review of the results

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obtained by efforts to reproduce the disease in experimental animals, a brief discussion of traumatic arthitis, and a consideration of certain mechanical factors which I believe influence the origin and progression of clinical hypertrophic arthritis.

THEORIES AS TO THE ETIOLOGY OF HYPERTROPHIC ARTHRITIS

One of the fundamental questions in the problem of hypertrophic arthritis is: Where does the disease begin? The pathologists of the last century found various answers to this question in the specimens which they examined. Rokitansky concluded that the primary change was an inflammatory osteoporosis in the subchondral bone which was followed by a sclerosis with secondary degeneration of the cartilage. Ziegler believed that the primary pathologic change was an atrophy of the subchondral bone and that this was followed by a loosening of the articular cartilage. Weber, on the other hand, regarded the cartilage changes as secondary to an abnormal calcification in the border zone between the bone and cartilage. Hein considered chronic arthritis a nutritional disturbance in the hyaline cartilage and Rimann believed that the joint changes were the result of some chemical alteration in the tissue fluids caused by tuberculosis, syphilis, cachexia, or arteriosclerosis. Volkmann believed that the disease was primarily a chronic inflammation of the synovial membrane and that this was followed by a secondary ossifying hyperplasia of the articular cartilage.

From the above paragraph it is evident that the study of pathologic material has led profound students of bone and joint pathology to widely different conclusions and that the subchondral bone, transition zone, articular cartilage, synovial membrane, and tissue fluids have each been considered the starting point of the disease process.

More recent authors have endeavored to explain the etiology of the disease. One of the most plausible of these is Weichselbaum[5] who made an exhaustive study of the joints of senile individuals and concluded that chronic hypertrophic arthritis was merely a high degree of these changes in the involved joints. But no explanation is offered as to why the changes occur early in certain joints and in certain individuals.

Wollenberg[6] modified the theory of Hein that the disease is due to a nutritional disturbance in the joint cartilage to the extent that this nutritional disturbance is in the nature of an ischemia due to local arteriosclerosis and that the arthritis is primarily a vascular disease in which the joint changes are secondary to the local vascular sclerosis.

Axhausen,[7, 13] as a result of some experiments to be mentioned below, concluded that cartilage necrosis is the primary cause of the disease and that the presence of dead cartilage in the joint exerts some influence, possibly chemical in nature, which leads to the development of the classical disease picture.

Preiser,[8] from an extensive study of clinical cases, concluded that incongruity of the joint surfaces results in local cartilage degeneration from relatively abnormal pressure and anemia, and that this leads to the further

development of the symptom complex of hypertrophic arthritis. Likewise, Nichols and Richardson,[9] from their pathologic studies, regarded long continued abnormal pressure with resultant cartilage degeneration as an important factor in the etiology of many of their cases.

Beneke[10] is usually considered to be the founder of the mechanical functional theory. From his studies on spondylitis deformans he concluded that the primary change was a degeneration of the intervertebral discs and that the changes in the vertebrae were the result of the continuous mechanical trauma incident to normal use in the presence of the degenerated discs. This theory has been slightly modified by Pommer[11] to the effect that the primary change is a loss in elasticity of the articular cartilage and that the disease is the result of repeated trauma to the underlying and now insufficiently protected bone.

Goldthwaite[12] has been the chief exponent of the mechanical theory in this country and attributes the development and progress of the disease to faulty body mechanics and abnormal strain on the involved joints. His great contribution has been the emphasis placed upon the patient as a whole rather than upon the local manifestations of the disease and his insistence upon the correction of faulty bodily mechanics, not only to relieve local strain upon the involved joints, but also to improve the general physiology of the patient and especially as a means of bettering the function of the abdominal and thoracic viscera.

EXPERIMENTAL HYPERTROPHIC ARTHRITIS

During the past twenty years a number of investigators have produced the changes characteristic of hypertrophic arthritis in various ways. In this paper we are primarily concerned with those in which the changes result from a definite injury to the joint. Among the first of these were the experiments of Axhausen[7] who killed a part of the joint cartilage in the knees of experimental animals by the application of iodine or ammonium hydroxide and produced pathologic changes which resembled those present in advanced hypertrophic arthritis. A few years later, in order to eliminate the chemical factor, he produced similar changes by cauterizing the surface of the cartilage with an electric needle. He believed that the development of the arthritis was due to the presence of the dead cartilage in the joint. (Axhausen.[13])

Wollenberg,[14] in attempting to prove his vascular theory, passed silk ligatures through the tissues around the patella in order to shut off the blood supply and after six months he found degenerative and hypertrophic changes in this bone. He interpreted the results as being due to local ischemia and thus accepted his experiments as proof of his vascular theory.

Axhausen and Pels[15] repeated Wollenberg's experiments and believed that the arthritic changes were due to the cartilage necrosis rather than to the ischemia.

Recently Pemberton and Goldhaft[16] have again repeated the experiment and adopted Wollenberg's interpretation of the results.

Kroh,[17] stimulated by the clinical observations of Preiser, resected one condyle of the femur in rabbits and found that arthritic-like changes devel-

oped in the joints. His joints were not studied histologically, but he believed that the experiments proved Preiser's theory that arthritis is due to incongruity in the joint surfaces.

Manteuffel[18] produced arthritic-like changes by freezing the knee joints of guinea pigs with an ether spray and by passive hyperemia. He did not consider the arthritis as being a result of vascular sclerosis, but thought that it was due to some other and as yet obscure cause.

Sury,[19] by repeated forcible manipulations or by percussion with a reflex hammer, produced degeneration and loosening of the cartilage with vascular sclerosis and ossification. He believed that he had produced a true traumatic arthritis.

Muller,[20] by suturing the humerus of rabbits to the scapula, immobilized the shoulder in such a manner that the tendon of the biceps remained constantly pressing upon the cartilage of the humerus. Under these conditions the cartilage became eroded and arthritic-like changes developed in the bone. From this experiment he concluded that the arthritis was due to abnormal pressure on the cartilage.

Wehner[21] resected the patella in a series of rabbits and found that arthritic-like changes resulted. He believed that his experiments showed that the arthritis was due to abnormal use of the joint.

Burkhardt[22] repeated Axhausen's experiments with carbolic acid and iodine and added the factor of immobilization in order to determine whether or not function was concerned in the development of the pathologic picture of arthritis deformans. In the joints which were used the picture of arthritis deformans developed in from three to five months while in the joints which were immobilized the cartilage remained intact for a long time and was gradually replaced by connective tissue and new cartilage which in some instances caused the joint to be filled with a cartilaginous connective tissue and tended to produce ankylosis with a picture resembling that of atrophic or gonorrheal arthritis. He found that villi developed in used joints while pannus developed in the immobilized joints and concluded that arthritis deformans is a regeneration phenomena which is due to cartilage injury and takes its anatomical characteristic from the mechanical function of the involved joint.

Carey (E. J., personal communication) tells me that he has found arthritic changes in the joints of dogs which were exercised over long periods in a treadmill.

I have produced mild arthritic-like changes in the knee joints of rabbits by the injection of mild irritants (Key[23]) and more recently I have shown that the pathologic picture of hypertrophic arthritis can be produced in the knee joints of rabbits by resecting a small rectangle of cartilage from the patellar surface of the femur. (Key.[24])

A simple method of testing the mechanical theory would be to create an abnormal strain on a joint which was in other respects perfectly normal. This I have attempted to do by the production of knock-knee in a series of twelve young rabbits. The method was to anesthetize the animal and simply

bend their legs outward at the knee over the edge of the table. By repeating the manipulation at weekly intervals over a period of weeks it was possible to obtain permanent valgus deformities of about 30 degrees. Seven of these rabbits grew to adult life and in each of these there was definite chronic

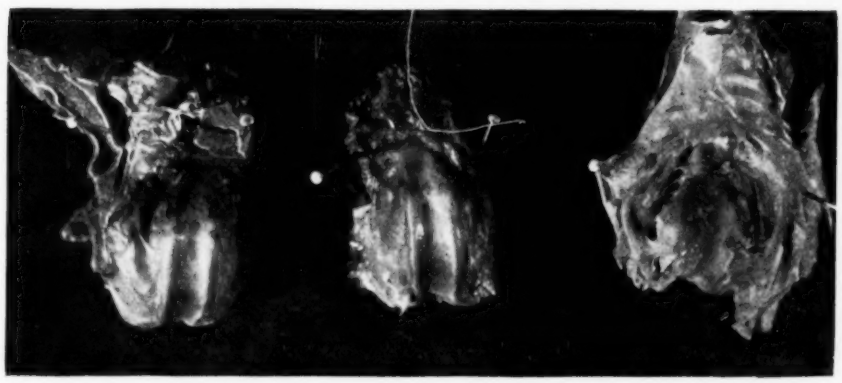

Fig. 1.—Photograph of lower end of the femurs and soft parts of rabbits in which valgus deformities were produced by manipulation. All showed injuries to the bones or ligaments and the arthritis was proportional to the injury.

Fig. 2.—X-rays of knees of rabbits illustrated in Fig. 1.

arthritis of the hypertrophic type with osteophytes around the cartilage margin, more or less hypertrophy of the involved bones and some hyperplasia of the synovial membrane. The most marked changes were found in those in which the patella had been displaced outward and rested upon the lateral surface of the femoral condyle. However, the value of these experiments is lessened by the fact that all of the knees showed evidence of definite articu-

lar damage which had occurred at the time of the manipulation. Either the lower end of the femur had been fractured, the femoral epiphysis had slipped, or the crucial ligaments had been ruptured. In other words in these animals what was produced was traumatic arthritis from a disorganization of the

Fig. 3.—Hallux rigidus due to an old contusion of the articular cartilage. Note the almost complete absence of the cartilage at the metatarsophalangeal joint.

joint or cartilage and bone injury and not chronic arthritis as a result of faulty mechanics in weight-bearing. (Figs. 1 and 2.)

From the foregoing it is evident that the pathologic changes characteristic of hypertrophic arthritis can be produced in many different ways.

TRAUMATIC ARTHRITIS

Let us now consider trauma as a factor in the production of chronic arthritis in man. The injury may be of several types: (1) a single severe injury to the joint cartilage; (2) repeated mild trauma to the joint cartilage;

Fig. 4.—Traumatic arthritis following an old injury to the internal semilunar cartilage and anterior crucial ligament. Note the narrowing of the joint space, roughening of the cartilage and the osteophytes over the internal condyle.

(3) disorganization of the mechanics of a joint; (4) faulty weight-bearing on account of bony deformity so that use brings about repeated injury to the joint surface; (5) gradual deformity of a joint by abnormal pressure.

1. An example of an arthritis resulting from a single injury to the joint cartilage is shown in Fig. 3 which is the x-ray of the toe of a man fifty-one

years old who violently kicked a tree while running after a ball twenty-five years ago. Apparently there was no fracture as there was no prolonged disability, but the toe was sore, swollen, and painful on motion for a few days. The metatarsophalangeal joint has been the site of occasional pain off and on for years and during the past five years the symptoms have grown steadily worse. Examination revealed a hallux rigidus with only a few degrees of motion and pain at the limits of motion. The x-ray shows evidence of almost complete absence of the articular cartilage and considerable production of new bone around the joint. In other respects the patient is normal and there is very little arthritis in any other joint. I believe that the arthritis in this joint is due to the old injury with contusion and degeneration of the cartilage. This belief is strengthened by the fact that I have seen three other cases of hallus rigidus with almost identical histories and physical findings.

2. Fig. 4 is an x-ray of a knee joint of a woman who had an injury to her internal semilunar cartilage and anterior crucial ligament twenty-five years ago. From time to time since the original injury the knee has locked or caught on her while walking or exercising and on some of these occasions the joint became swollen and she was disabled for some weeks. At one period she was free from symptoms over a period of fifteen years. During the past two years the pain and catching have been largely limited to the region of the posterior portion of the external semilunar cartilage.

At operation the internal semilunar was found to be markedly degenerated, all that was left being a thin outer rim with several loose fringes of fibrous tissue hanging into the joint. The cartilage over the internal condyles of both bones was roughened and fibrillated and partly eroded, and the cartilage over the external condyles showed slight roughening. The external semilunar was abnormally loose, the anterior crucial ligament was absent, and there were numerous osteophytes around the articular margin of the femur and the fat pad and synovial membrane were moderately thickened.

I believe that the repeated mild injury caused by the loose or torn internal semilunar cartilage and torn crucial ligament caused the degeneration of the cartilage of the internal condyle and that this resulted in the osteophytes and synovial thickening.

3. Chronic arthritis as a result of disorganization of the mechanics of a joint is all too frequently seen after joint fractures in which the fragments have been imperfectly reduced and permitted to unite with more or less inexact restoration of the normal contours of the articular surfaces. A very familiar type is the traumatic arthritis of the knee seen after compression fractures of one or both condyles of the tibia. If the depressed fragment is large a genu valgum or varum may result and the insult of the abnormal weight-bearing is added to that of the inequality in the cartilage, but if the fragment is small the line of weight-bearing is not disturbed. However, even with a small portion of the lateral condyle depressed only ⅛ of an inch I have seen chronic arthritis develop in the knee of a man thirty years of age and lead to so much disability that an excision and arthrodesis of the joint would be preferable.

Other shining examples are fractures of the head of the radius or of the neck of the radius with displacement of the head. In many of these cases early removal of the radial head will prevent the development of the arthritis and give the patient a useful painless elbow. A very striking example of this type of arthritis is seen in the hip after a Legg-Perthes disease in childhood or a slipping of the upper femoral epiphysis in adolescence. In the former the femoral head and acetabulum are deformed and in the latter the displaced head of the femur no longer fits in the acetabulum. Practically all of these patients have pain and limitation of motion in the hip after they

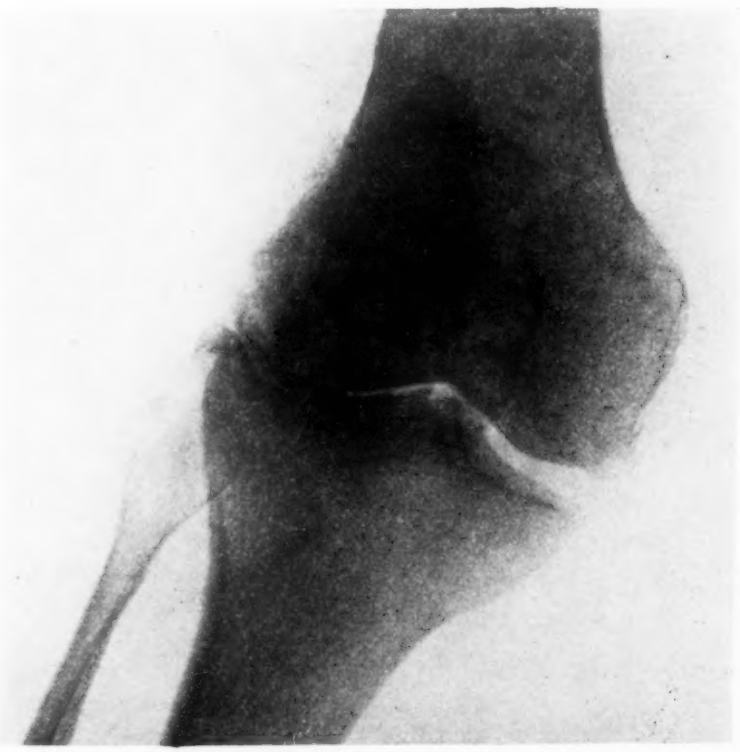

Fig. 5.—Severe hypertrophic arthritis in a woman seventy years old in whom a genu valgum had been present since childhood. Note the complete disappearance of the cartilage eburnation of bones and osteophytes over the external condyle.

reach adult life, and it is my belief that these mechanical defects in the hip acquired in early life are the cause of most of the so-called Malum Coxae Senilis (Key[25]). Frequent examples are seen in the ankle and subastragaloid joints after fractures at the ankle or of the os calcis and others are seen at the wrist after typical extension and compression (Colles), or other types of fractures of the lower end of the radius.

I have also seen traumatic arthritis develop in a joint after a fracture which had been apparently perfectly reduced, but as a rule the degree of disability and arthritis vary directly with the amount of displacement, especially in weight-bearing joints.

4. A good example of an arthritis developing in a joint which has been subjected to prolonged abnormal strain is shown in Fig. 5. It is an x-ray of the knee of a woman seventy years of age who had had a rather severe bilateral genu valgum since childhood. Note the disappearance of the cartilage over the external condyles (points of abnormal pressure) and the marked arthritic changes throughout the joint.

In extraarticular fractures particularly of the femur or bones of the leg which are permitted to unite with deformity the knee and ankle joints are subjected to abnormal strains and in early adult life tend to develop a

Fig. 6.—Arthritis of the knee in which a valgus deformity followed an old injury. Note the eburnation and osteophyte formation on the external condyles.

chronic arthritis which is almost identical with the hypertrophic arthritis of late adult life except that it affects only the involved joints. Fig. 6 is an x-ray of a man thirty-five years old who had been kicked by a horse fifteen years previously with probably a fracture of the lower end of the femur. He had a valgus deformity of 45 degrees and a compensatory varus deformity at the ankle with moderately severe hypertrophic arthritis in the knee.

5. The classical example of an arthritis developing as a result of long continued abnormal pressure is seen in the arthritis of the first metatarsophalangeal joints which is present with hallux valgus and bunions (Fig. 7). The deformity is usually the result of short shoes and the (bunion) hypertrophy of the metatarsal head is partly the result of abnormal pressure from

the shoe, partly of irritation at the insertion of the internal lateral ligaments caused by the toe being pushed outward, and partly the result of the arthritis in the joint which in some as yet unknown manner causes overgrowth of bone. That this last factor may be important is evident from the frequent lipping and exostoses which are seen on the dorsal surfaces of the involved bones.

It is thus evident that various types of intraarticular injuries or mechanical insults may result in chronic arthritis.

Fig. 7.—Typical bunion formation. Note the disappearance of the cartilage over the first metatarsophalangeal joint and the newbone formation around the head of the first metatarsal.

CLINICAL HYPERTROPHIC ARTHRITIS

Pathologically this disease is characterized by degeneration of the cartilage and eburnation of the bone over the bearing surfaces of the joints with the production of osteophytes around the articular margins and a variable amount of hyperplasia and infiltration of the synovial membrane and subsynovial tissues.

The disease comes on after middle life and is particularly apt to affect the heavy type of individual and to be localized in the large weight-bearing joints and in the terminal interphalangeal joints of the fingers. It is more common among people who have performed much hard manual labor or who have static deformities which have placed unusual strain upon the involved joints.

One of the most interesting features of the disease is the fact that often there is no apparent relation between the extent of the pathologic changes

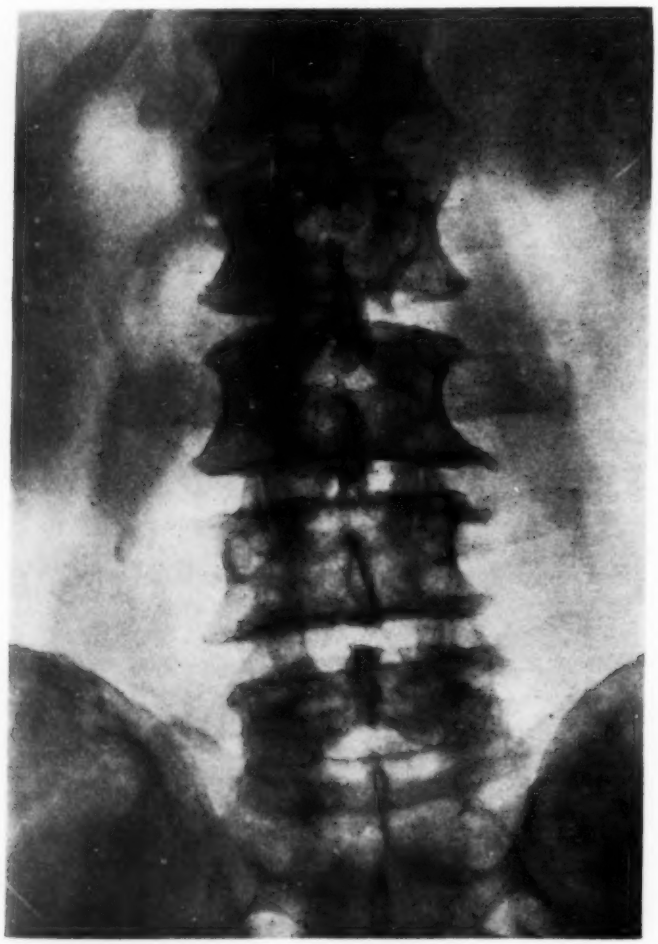

Fig. 8.—Typical hypertrophic arthritis of the lumbar spine. Note the relatively broad, flat vertebral bodies and the osteophyte formation at their margins.

and the severity of the clinical symptoms. In many cases extensive pathologic changes may be present in a joint over a long period of years and cause practically no symptoms and the patient may not be aware that there is anything wrong with his joints. On the other hand another patient may have considerable pain and disability in a joint which is practically normal to x-ray and clinical examination. Not only are the joints painful, but there

may be pain and tenderness over the adjacent bones, particularly along the crest of the tibia in arthritis of the knee. Generalized muscular pain and stiffness are also frequent in patients in whom the joints are causing symptoms.

In many cases the symptoms vary with the weather and these patients usually feel worse with a fall in barometric pressure. In others the symptoms come and go without rhyme or reason and occasionally a mild injury to a joint may inaugurate a long period of pain and disability.

In examining patients with hypertrophic arthritis we are accustomed to look for static defects which may be a factor in the etiology of the disease. And quite frequently we find such defects. A common example is seen in the heavy women over fifty years of age with hypertrophic arthritis in the knees. In such patients the feet are usually pronated and the knees show a slight valgus deformity. We believe that one important factor in the development of the condition in these patients is the faulty mechanics at the knee joint with abnormal strain on the internal lateral ligaments and abnormal pressure on the external condyles with consequent injury to the articular cartilage. The abnormal strain and pressure are particularly evident in walking: as the foot and ankle are turned outward and as the knee is flexed the inner side of the joint tends to open with consequent irritation at the sites of attachment of the internal lateral ligament and abnormal pressure on the external condyles.

Much the same mechanism is at work in the spines which are the subject of this type of arthritis. The vertebral bodies in these spines are usually of the broad relatively short type and due to their shape the amount of motion between the bodies of the vertebrae is much greater for a given amount of bending than occurs in a spine with relatively narrow long bodied vertebrae (Fig. 8). As a result the amount of motion in these heavy type spines is less than is normal for the slender type spine and the performance of a given amount of motion imposes a greater strain on the intervertebral ligaments on the convex side and abnormal pressure on the discs on the concave side of the curve. To this chronic irritation the bone responds by the production of the osteophytes around the vertebral margins which are the characteristic feature of the disease. In addition to the handicap mentioned above, the spines of the heavy type individuals are usually placed under abnormal static strain as these people tend to develop pendulous abdomens, and in order to support the abdomen, they lean backward at the lumbar and lumbosacral regions with the development of an abnormal lumbar lordosis and a later compensatory dorsal kyphosis and round shoulders, thus placing an abnormal static strain on spines which are mechanically unfitted for a wide range of movement.

Frequently the symptoms in these patients can be relieved by supporting and resting the involved joints and protecting them from abnormal strain.

On the other hand we occasionally see comparatively young patients with definite hypertrophic arthritis in whom the general health is excellent and the body mechanics are unusually good, and we have learned that we are apt to have considerable difficulty in relieving such patients of their symptoms.

Heberden's Nodes.—In addition to the group of patients in whom no mechanical defects can be found to account for the disease there are two very common conditions associated with hypertrophic arthritis which have not yet been explained on a mechanical basis. The most frequent and characteristic of these is the involvement of the terminal interphalangeal joints of the fingers with the development of the enlargements which are commonly called Heberden's nodes and progressive degeneration and deformity of the joints. The development of clubbed fingers in patients with chronic heart disease or suppuration in the lungs with insufficient aeration has led some observers to regard the Heberden's nodes as due to either bacterial or metabolic toxemia and others to regard them as the result of an insufficient supply of arterial blood. But anyone who has compared Heberden's nodes with a clubbed finger must have been struck by the obvious difference between the two conditions. The clubbed finger is a uniform hypertrophy of the entire terminal phalanx, bone and soft parts; while the Heberden's node is a production of new bone, cartilage, and fibrous tissue around the base of the phalanx with degeneration of the articular cartilage. Furthermore the Heberden's nodes are frequently not only tender, but may be the site of spontaneous pain and swelling and may be red and resemble an inflammatory lesion either from infection or some toxin or chemical irritant. No stretch of the surgeon's imagination has yet succeeded in attributing the localization of the arthritis in the terminal interphalangeal joints to mechanical causes except in rare instances where they are thought to be occupational.

Subdeltoid Bursitis.—A second very characteristic condition which is prone to develop in individuals who are affected with chronic hypertrophic arthritis and which cannot be explained by faulty mechanics is that frequent but poorly understood symptom complex which is variously called subdeltoid bursitis, periarthritis of the shoulder, or merely stiff and painful shoulder. Codman has shown that some of these stiff and painful shoulders are due to traumatic rupture of the tendon of the supraspinatus muscle, but this is quite a rare injury, and as a rule we do not know even where the pathology is located, though in the majority of cases we are inclined to incriminate the subdeltoid bursa. In some cases the onset is either sudden or insidious and without known cause and resembles a true infectious or toxic lesion, while in others the symptoms follow a definite injury, particularly a blow or fall upon the shoulder, and in still others the cause seems to be occupational. However, in practically no case can the localization of the symptoms in the shoulder be explained by the mechanics of the joint, though it must be admitted that postural enthusiasts are prone to do this when they discover the condition in a round-shouldered patient.

DISCUSSION

From the short review of the literature on experimental arthritis in the early part of this paper it is evident that a condition resembling clinical hypertrophic arthritis can be produced in the joints of experimental animals by various methods which result in injury to the articular cartilage, either di-

rectly or through the production of incongruities in the joint surface with the result that the cartilage is injured by the function of the joint. And it has also been shown that the simple removal of a small portion of the cartilage leads to the same changes.

Likewise the section on traumatic arthritis in man indicates that if the cartilage of a normal joint is subjected to severe injury or to repeated mild trauma from incongruity of the joint surfaces or abnormal function, a condition quite similar to hypertrophic arthritis may be expected to develop in the injured joint.

Finally in the section on clinical hypertrophic arthritis the fact has been emphasized that the condition is most often seen in the joints of heavy people who are beyond middle life and that it is especially common in joints which, because of static defects, have been subjected to abnormal strains over a period of many years and that the symptoms are often relieved by correction of the static defects.

The three preceding paragraphs suggest that hypertrophic arthritis is simply a worn-out joint and that the pathologic picture presented by these joints largely represents the reaction of the joint to an injury and that continued function of the injured joint is necessary for the production of the typical reaction. But a more careful consideration of the disease leads one to the conclusion that such a simple explanation does not suffice and that an answer to many of the questions which confront the student of the disease lies far deeper and must be sought in the individual as a whole rather than in the involved joint.

In other words the joint is a point of lowered resistance where some generalized condition becomes manifest. What this condition is we do not know. Plausible suggestions are: low grade infection, vitamin deficiency, some as yet unknown abnormality in the general metabolism, vascular disease of unknown etiology, and absorption of toxic material from the intestine or from foci of infection. It is possible that there are several causes and that one acts in one patient and another in another patient.

In this paper I have not attempted to prove the mechanical functional theory of the disease, but have merely tried to emphasize the facts that the pathologic picture of hypertrophic arthritis can be produced by mechanical insults to a joint and that in many cases the symptoms can be relieved by rest and the correction of static defects. We are still seeking the ultimate cause of the disease.

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THE BRITISH RED CROSS SOCIETY'S CLINIC FOR RHEUMATISM

By A. R. Neligan,* M.D., London, England

THE Clinic was opened in March of the present year for the treatment of persons suffering from the group of diseases loosely covered by the name "chronic rheumatism." The story of its origin is as follows:

Chronic rheumatism has long been known as a cause of serious invalidity in the British Isles. Individual workers on its problems have been numerous, and much good work has been done at the Mineral Water Spas, but no concerted action had been taken as in the case of tuberculosis, cancer, and venereal disease.

In 1923, however, the British Ministry of Health published a report on "The Incidence of Rheumatic Diseases." This for the first time opened the eyes of the public and the medical profession to the serious economic and health problems which rheumatism presents.

In 1925 a sub-committee of the International Society of Hydrology was formed to study these problems in different countries, and later a British Sub-Committee was formed. The Approved Societies, composed of industrial workers, which provide sick insurance under the National (or State) Health Insurance Acts, by now alive to the great inroads which chronic rheumatism among their members was making on their funds, entered keenly into the investigation. Visits were made by laymen and doctors to European countries, and the information brought back showed that in several of them, more especially in Germany and Austria, there were well equipped clinics in some of the large industrial centers for treating workers suffering from rheumatism; also that government authorities, industrial, charitable and other organizations had combined in providing facilities at the different spas and health resorts.

In 1927 the British Committee on Rheumatism put forward a scheme for a Demonstration Clinic in London, equipped with the different methods of physical treatment, and capable of dealing with several hundred patients a day. The hope was expressed that, if successful, the Clinic would be followed by others. The proposal had a good reception, was well supported by the press, and received the blessing of the Ministry of Health. The question then arose as to who should take it up. Fortunately the British Red Cross Society was found ready to do so. It may be noted here that, since the Great War, the Society, like the United States Red Cross Society, has organized to exercise its beneficent activities in peace as well as in war.

The first question was that of a site for the projected Clinic; it had to be central and with first-rate communications. The first essential was not easy to satisfy in overcrowded London, except at prohibitive cost, and it was eventually decided to convert a very large disused Baptist Chapel for the purpose required. This building put up in 1825 as a panorama was, two years later,

*Medical Superintendent.

turned into a Chapel and remained one up until 1922. Just at the southeast corner of Regent's Park, its communications are first-rate by main line and underground railway, and numerous omnibus routes.

The cost of converting and equipping the building was estimated at £40,000 and this was quickly collected by public subscription. When the Chapel was first taken over, the baptismal pool was plain to see, and the legend sprung up that the deep pool baths which were eventually made in the bath section of the Clinic, were none other!

Work was begun early in 1929 and was completed about a year later, though improvements are still being made. Many difficulties were met with in convert-

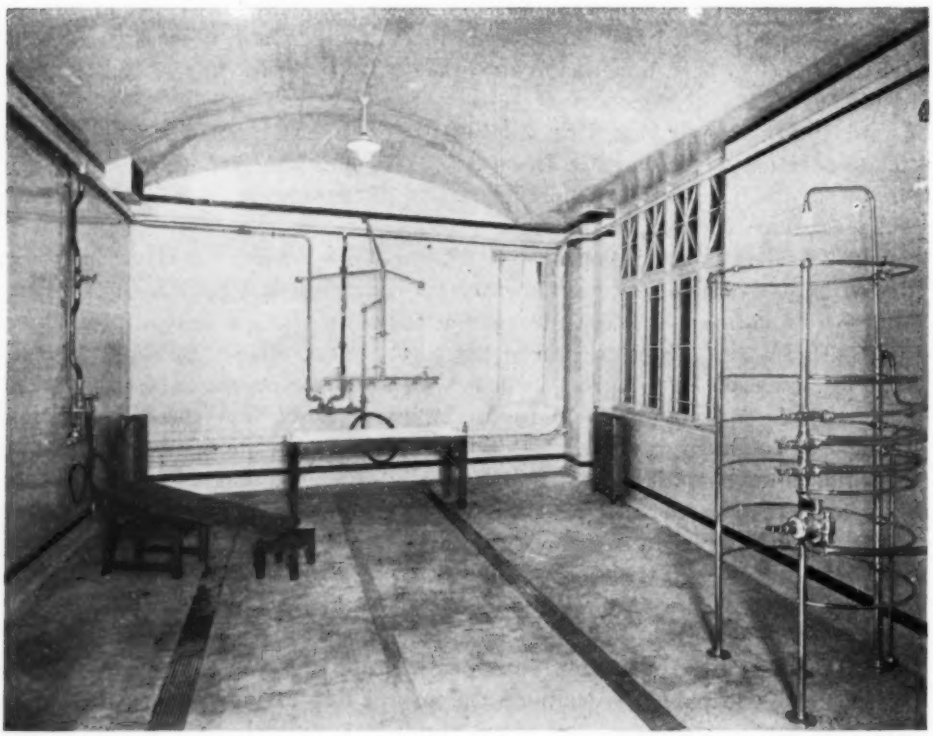

Fig. 1.—Hydrotherapy section: massage, douche apparatus and needle bath.

ing an old building, with houses on either side, for its outer walls were retained, and they have left their mark on the internal arrangements.

Her Majesty the Queen opened the Clinic formally on February 25 of this year.

Construction and Equipment.—The Clinic is now a three floored structure, pierced by a central octagonal shaft, twenty-two feet across, running from the ground floor to a glass dome, for purposes of light and ventilation.

The ground and first floors are given up to patients who can pay only small fees; the second floor is for private patients.

On the ground floor are the Admission Office and Waiting Room and the

Lady Almoner's Offices (she corresponds with the head of the Social Service Department in the United States). The rest of the floor is given up to hydrotherapy.

In the center of the octagon mentioned, and immediately beneath the glass dome 50 feet above, is a circular pool, 16 feet in diameter and 4 feet deep. This is divided into two equal halves, and one of the halves again divided, so that there are three baths; one large (2416 gallons) which is kept at a temperature of 98° F. and two small at 100° and 102° F. Each pool has a thermostatic blender for delivering a constant supply of water at a fixed temperature; the

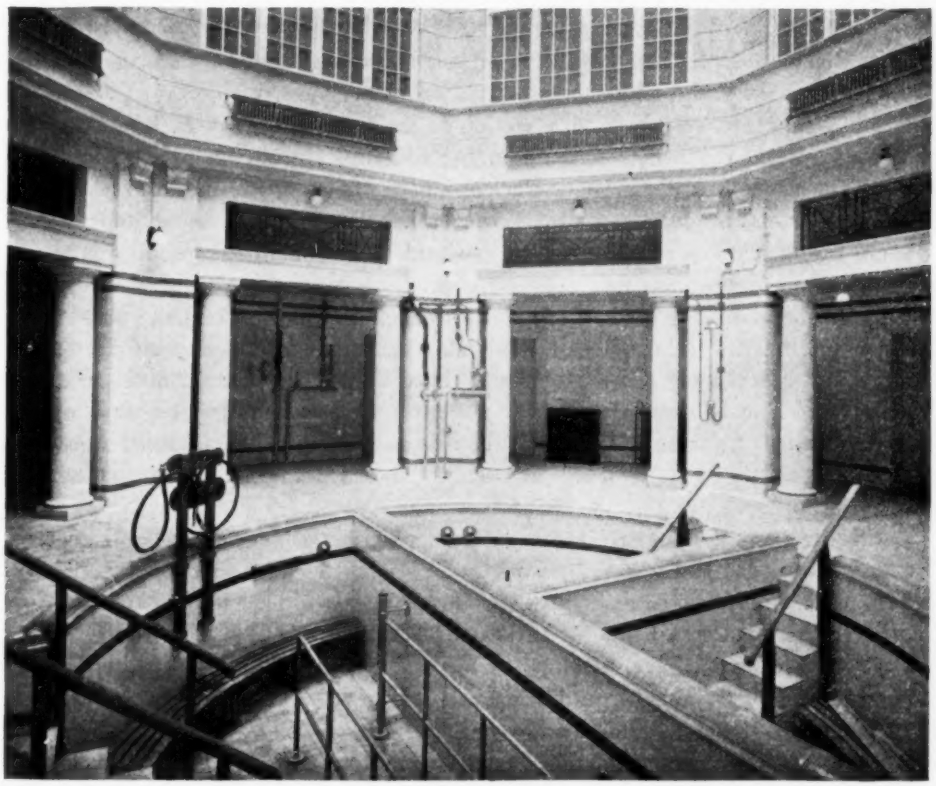

Fig. 2.—Hydrotherapy section (ground floor): parts of the pool baths.

overflow leaves the bath through standing waste pipes 3 feet 6 inches high. The baths have teak seats, on which a patient can sit comfortably with his chin above water. In the large bath there are parallel bars to enable patients to exercise their lower limbs. There is also a thermostatic blender at the side of this bath for underwater douching at a temperature 5° to 10° higher than that of the pool itself, a very useful form of treatment in old muscular and joint conditions. The pools are also used for free exercises, graduated movements and reeducation of muscles, and manipulation by masseurs, who enter the water with the patient.

The floor surrounding the pool is paved with ribbed tiles to prevent patients slipping, and is heated.

From the central octagon open the dressing boxes (20), two large bays for different water treatments, a hot air room (Turkish Bath) and a vapour room (Russian Bath), with shower nearby; a linen room with hot cupboards, and a room for the masseurs. Reached by a short passage there is a rest room where patients lie on couches, wrapped in a warm sheet and blanket, after treatment, for half an hour or longer. The same corridor leads to the lavatories.

The equipment in the two bays mentioned consists of baths and douches. In the first bay are four shower and foot baths where patients wash before treatment; two reclining baths, both fitted with underwater douches, and one with an aeration equipment; one teak bath for brine baths; one whole body whirlpool bath; and a Scotch douche.

In the second bay is a needle bath, and the equipment for massage douche baths by the Aix and Vichy methods, two of each.

The temperature in this bath section is maintained at 70° F. by means of radiators around the walls, high up in the octagon, and steam pipes below the floor. The walls are white tiled, the coping of the pool is blue, and with the gleaming chromium-plated apparatus the bath hall gives a pleasing impression.

On the first floor, reached by lift or stairs are: consulting room, examination and booking rooms; two rooms for treatment by massage and electrical methods; one room for carbon arc light treatment; an x-ray room; and room for colonic lavage. The offices of the Medical Superintendent and Sister-in-Charge and a room for the masseuses. There is also a rest hall, and the main linen store. The two main "dry" treatment rooms are equipped with the different varieties of galvanic, faradic and sinusoidal currents, diathermy, luminous and nonluminous radiant heat, ultra-violet light, massage apparatus and a shower bath.

On the second floor private patients are given consultations and receive treatment by practically the same methods as on the ground floor. The only difference is that they have greater privacy. The two deep pool baths are, for instance, individual, and not for several bathers.

On this floor is the clinical laboratory equipped for all the ordinary bacteriologic and biochemical examinations.

In an annex on a higher level than the second floor there are offices for the secretary and accountant, and a tea room for the staff. This leads on to a flat roof, where whatever sun is vouchsafed to London can be enjoyed, with a view of many housetops and the green heights of Hampstead and Highgate in the distance.

On the roof are placed the water storage tanks, seven in all, of one thousand gallons each.

The water used for treatment is ordinary London water which has been softened on the premises. The heating plant is by two vertical steam boilers with two 300 gallon calorifiers.

The electricity supply from the main is direct at 240 volts. This is stepped down for treatment purposes to 100 volts, and also converted into alternating current at 100 volts, in the switch room.

It will be noted that there is no mention of beds; the Clinic is designed for the treatment of ambulant patients only.

Patients.—While the Clinic has been founded to help the industrial worker in particular, all classes of patients are accepted, provided they bring with them from their medical attendants a certificate to say that they are suffering from rheumatism. All are expected to pay towards the cost of their treatment, for the Clinic has no endowment fund and it is hoped that it will become self-supporting.

As regards the poorer class of patient, they are divided into two groups:

1. Noninsured persons; their fees are arranged by the Lady Almoner to suit their circumstances. A certain number of free cases naturally are accepted.

2. Insured persons; that is to say contributors to the National Health (or State) Insurance Scheme. They are in most cases members of "Approved Societies" and these have received authority from the Ministry of Health to pay out of their funds, a capitation fee of three shillings (75 cents) per treatment, or 25 shillings for a course of 9 treatments. This sum covers consultations but not drugs (provided under the Act). X-ray examination is counted as a treatment.

These are trial figures which may be adjusted in the future. The Clinic is the only institution recognized by the Ministry for the purpose, and the payment is not yet authorized by law as in the case of the "additional benefits" for specialist treatment of the teeth or eyes. It is expected, however, that if the Clinic is a success the treatment of rheumatism at institutions approved by the Ministry will be made an additional medical benefit under the Insurance Act.

Here again the patient is accepted for treatment only on the recommendation of the insurance general practitioner on whose "panel" he is.

A number of charitable organizations and Friendly Societies are seeking and obtaining the same arrangements for their members.

Private patients pay roughly ten dollars for their first and five for subsequent consultations. These fees go to the Visiting Physicians. The charge for each attendance for treatment is roughly two and a half dollars paid to the Society.

All patients must be seen and all treatment prescribed by a member of the Staff. Consultations and treatment are given by appointment only.

Treatment is given to the two sexes on alternate days between the hours of 9:30 A.M. and 8:30 P.M. A special feature is being made of evening consultations and treatment out of hours for day workers. This is much appreciated and would seem to be the only way of getting early and slight cases to pay attention to their condition.

The Medical Staff of the Clinic consists of five visiting physicians who are specialists in treatment by physical methods, or general physicians interested in the rheumatic group of diseases. Each attends twice a week to see patients. The Surgical Staff of the Clinic is supplied by the Royal National Orthopedic Hospital which is hard by. There is a pathologist and a radiologist. Other specialists are in course of being appointed.

The Nursing Staff consists first of the Sister-in-Charge, who is a trained nurse as well as a qualified masseuse. She has two assistants and a staff of 4 masseuses for the dry treatment rooms and 16 masseuses for the bath section;

some of the latter are students in hydrotherapy. There are eight bath masseurs, some again of whom are students. All treatment assistants and students have the certificates of the Chartered Society of Massage and Medical Gymnastics, which demands a two years training in anatomy, physiology, massage, remedial exercises, and medical electricity. The Society has the intention of introducing a certificate in hydrotherapy, and the Clinic will be a training school for it.

On account of the long hours during which the Clinic is open, many members of the treatment, social service and administrative staffs have to be duplicated, and this adds greatly to the running costs. It is estimated that these will amount to some £15,000 a year.

Consultations are held morning and afternoon and three times a week in the evening between 5 P.M. and 8 P.M. Treatment is carried on daily from 10 A.M. to 1 P.M. and from 2 P.M. to 8 P.M. or later. The provision of evening consultations and treatment after work hours is held to be essential to any scheme of dealing with the problem of industrial rheumatism.

The *responsibilities* accepted by the Clinic are as follows:

1. Diagnosis.
   Selection of cases for spa, hospital and other outside treatment.
2. Treatment.
3. Follow up and welfare work.
4. Education of:
   - Medical students.
   - Postgraduates.
   - Treatment assistants.
   - Patients (prevention).
5. Research into the causes, prevention, and treatment of rheumatism.

The *nature of the conditions* accepted for treatment is as follows:

1. Chronic rheumatic diseases:
   (a) Articular, i.e., chronic (nontubercuIous) arthritis, including spondylitis and gouty arthritis.
   (b) Nonarticular, i.e., lumbago and other forms of muscular rheumatism, sciatica, fibrositis, etc., etc.
2. Muscular weakness or paralysis, neuritis, neuralgia.
3. Sequelae of injury to or inflammation of joints, muscles, tendons, bones and nerves.

Types of Rheumatism.—Patients with rheumatism may be, from the point of view of treatment, divided into two great groups:

1. Those with definitely chronic disease, more or less fixed deformities and more or less pain.

2. Those in the early stages, the prearthritic, early rheumatoid or infective arthritis, early muscle and nerve rheumatism, and so on.

The latter class is well worth much time and care, continuous for months or years it may be; it is the class which best rewards effort, and should, where bed treatment is not necessary, be the special object of a clinic such as this.

For the first class little can be done in the way of permanent, but a great deal by repeated treatments in the way of temporary relief. Unfortunately this class is very numerous and very pitiful, and absorbs much energy and

time. It forms the bulk of our patients so far, and it presents this problem, well foreseen, which every clinic of this sort must face; how to prevent the clogging of the machinery of treatment by large numbers of advanced cases.

Another point which comes out is that women patients greatly exceed men. This is a common feature of treatment centers for rheumatism. The difference will be less marked as the Approved Societies take fuller advantage of the scheme, for the majority of insured workers are men.

Taking our statistics as far as they go, the cases fall roughly into three groups, the rheumatic, the medical and the surgical. The existence of the two latter groups shows that useful work is being done in diagnosis; in them have been found cases of central nervous lesions, appendicitis, metastatic newgrowth, orthopedic conditions, etc.

An analysis of rheumatic patients seen, shows that they were suffering from the following conditions, and in the proportions given. The numbers available are small, but they will serve to give some idea of the run of the clinical work. Decimal points have been omitted.

The Nonarticular conditions form 28 per cent of the whole, distributed in the following proportions:

	MALES PER CENT	FEMALES PER CENT	TOTAL PER CENT
Fibrositis	8	25	33
Lumbago	7	3	10
Lumbosacral conditions	7	3	10
Myalgia	7		7
Neuritis		10	10
Sciatica	22	3	25
Vague rheumatic symptoms		10	10

Arthritis accounts for 72 per cent of the whole, distributed in the following proportions:

	MALES PER CENT	FEMALES PER CENT	TOTAL PER CENT
Climacteric		5	5
Gouty	1	2	3
Infective	10	6	16
Ostearthritis	20	10	30
Prearthritic conditions	1	2	3
Rheumatoid arthritis		25	25
Spondylitis		1	1
Unclassified	1	10	11

Classification of Arthritis.—The term "rheumatoid arthritis" is being confined by the Medical Staff to cases of the atrophic type *in women*. "Ostearthritis" corresponds to hypertrophic arthritis.

Early Results.—First impressions point to the Clinic filling a real need. The small nucleus treatment staff with which a start was made has had to be progressively increased, and additional space and apparatus have had to be brought into use, to meet growing demands. Still further facilities are shortly to be provided. The applications for treatment are numerous and there is a long waiting list of women patients. In March (twenty days) there were 680 attendances for treatment, in April 1844, in May 4487. The average daily attendance has been 145. The following brief analysis gives an indication of the

numbers and kinds of treatments administered. Series treatments are commonly prescribed, two or three at an attendance.

Massage and electrical treatments: 2195 in the month of May.

Diathermy	745
Massage and Remedial Exercises	527
Infra Red Rays	250 (general)
Ultra Violet Rays	192 (general)
Schnee Bath	169
Radiant Heat	108
Galvanism	88
Faradism	87
Kromayer Lamp	21
High Frequency	8

Under "diathermy" are included general diathermy and pelvic diathermy (cervix and prostate). With the Schnee bath, surging sinusoidal and galvanic currents are given; rheumatoid conditions of the hands and feet and muscular wasting and brachial neuralgia have been the common indications. The treatment of certain types of infected tonsils and local rheumatic lesions, with the water cooled Kromayer lamp, is being tested.

BATH TREATMENTS: 5202 IN THE MONTH OF MAY

Reclining Baths:		
with aeration	180	
plain	64	
with underwater douche	44	
medicated	36	
	—	324
Pool Baths:		
with underwater douche	734	
with manipulation	28	
with free exercises	14	
	—	776
Massage douche—Aix method		636
Vichy method		351
Needle bath		1022
Scotch douche		315
Hot air room (130°-140°)		932
Vapor room (100°-104°)		231
Packs		73
Whirlpool bath		87
Colonic lavage		165
Massage after bath treatment		290

The reclining bath with aeration is useful as a tonic treatment for patients unable to stand the more vigorous forms of hydrotherapy, and as a method of "skin training." The medicated bath most used is the brine bath; sulphur and alkaline baths are occasionally ordered. The value of the pool or deep immersion bath, generally at 98° or 100°, and with underwater douching, in arthritis and fibrositis is well known. Aix massage douche baths are prescribed especially for local conditions, Vichy for more general treatment. They are preceded by five to ten minutes in the hot air room in order to stimulate the skin, and followed by a needle bath cooled to 80° or 70° F., hence the high numbers for these two forms of treatment. For local treatment by packs,

fuller's earth is used. Colonic lavage is given with a simple irrigator and an alkaline isotonic solution, to which potassium permanganate is occasionally added.

It will be seen from this brief résumé that, for the moment, treatment is centering round the hydrotherapeutic measures, except for diathermy and dry massage, both of which are much prescribed. The "heating" treatments, too, whether "dry or wet," radiant or nonradiant, are also high in the list.

As to the actual results of treatment, it is obviously too early yet to say much. It is quite certain that a large number of sufferers have been given relief as regards pain and disability for the time being.

It is estimated that when the additional accommodation and apparatus in view have been provided eventually more than 200 patients can be treated in the large bath section daily; 120 in the massage and electrical rooms; and 70 on the private floor.

Research.—If there is little to say on this subject, it must be remembered that the starting and organization of treatment in a new type of institution has been no light task. For various reasons, too, plans have had to be curtailed, but already data are being collected on the flora of the throat, and certain types of new treatment or modifications of old are being tested. It is intended that research into the causes of rheumatism shall receive full attention.

Rheumatism as an Industrial Disease.—The opening of the Red Cross Clinic marks, as has been said, the first step of a movement to provide on a large scale in England treatment for rheumatism, especially among industrial workers. Our own experience is too short to add anything to what is known already on the subject of industrial rheumatism, but it will not be inappropriate to accede to the editor's request and add a few lines on the subject, to what has already been said in the first part of this account. The facts and figures which follow are nearly all taken from the reports of the British Ministry of Health.*

The proportion of patients in industrial practices in England who suffer from rheumatism is roughly 5 per cent. (D. K. Brundage of Pittsburgh, U. S. A., made it 6.4 per cent among steel workers.) An estimate of insured workers in this country made in 1927 was, however, no less than 9.8 per cent.

The proportion of lost working days due to rheumatism (rheumatic fever included) is no less than one-sixth of the total caused by all diseases. In 1927 some 5,000,000 weeks were lost owing to this cause.

The cost of this huge mass of invalidity in sick pay was £5,000,000, and in addition £12,000,000 was lost in wages. "More than half of this great total of rheumatic sick absence for both sexes is due to chronic joint diseases, principally rheumatoid arthritis, and ostearthritis in nearly equal shares." The proportion due to nonarticular manifestations was one-third in men and one-quarter in women.

The average age of insured females is less than that of insured males; the following figures are, therefore, not strictly comparable. They show the expected attack rate per 1000 of the two sexes in a year.

*The Incidence of Rheumatic Diseases, 1924. Chronic Arthritis, 1928.

		MALES	FEMALES
Arthritis—	rheumatoid	1	3
	ostearthritis	3	2
	gout	3	0.1
	unclassifiable	1	
Muscular	rheumatism	6	7
Lumbago		10	3
Sciatica		3	1 (or brachial neuritis)

As regards occupational incidence, the Ministry's inquiry brought out the liability of metal workers to rheumatic disease; it is "nearly 80 per cent in excess of expectation." In steel works the puddlers are especially liable; alternating heavy work, exposure to heat and chilling of the body surface must have much to do with this. The tin-plate men on the other hand, working more or less continuously, do not suffer excessively. The effect of exposure to weather is shown in the liability of the London tramcar driver to rheumatism, especially if he has no protection. Exposure to heat in industry is not a predisposing cause, but if accompanied by damp, it is. These facts call to mind the importance of the skin functions in rheumatic subjects. It is, therefore, interesting to know that the provision of baths at coal mines has begun. In another direction the provision of dental treatment under the National Health Insurance Act should have an effect on the incidence of rheumatism among the working classes.

The figures given of working days lost and the cost to the community of rheumatism demand its closest attention, especially when it is, as in England, an industrial one. But they apply to the insured population alone, say 16,000,000 souls, and, further, they utterly fail to convey any adequate impression of the misery, the inefficiency, and the mental strain, for which rheumatism is responsible.

Surely chronic rheumatism is one of the major problems of medicine and perhaps the most difficult one of all.

PETO PLACE, MARYLEBONE ROAD, N. W. 1.

DEPARTMENT OF REVIEWS AND ABSTRACTS

ROBERT A. KILDUFFE, M.D., ABSTRACT EDITOR

ALLERGY: New Method of Administering Pollen Extract for the Purpose of Preventing Reactions, Duke, W. W. J. A. M. A. 94: 767, 1930.

The method of administering pollen described here is designed to control the rate of dissemination from the site of inoculation and depends on four important steps:

1. The placing of a rubber tourniquet around the arm above and just prior to the injection of the pollen, and its frequent removal and replacement for at least five minutes after the injection.

2. The admixing of epinephrine and ephedrine with the pollen solution in such dosage as to slow down its rate of dissemination from the site of injection.

3. The reducing of all doses to a given volume by an admixture of physiologic solution of sodium chloride.

4. The introduction of 0.01 c.c. of the pollen mixture subcuticularly, preliminary to the injection of the entire mixture. The appearance of a tiny blanched area will indicate that the needle is not in a vein and the entire mixture, if injected, will go into the subcutaneous tissues.

TUBERCULOSIS: Method for Rapid Demonstration of Tubercle Bacilli, Pfannenstiel, W. Deutsche. Med. Wchnschr. 55: 2130, 1929.

Pfannenstiel described a method by means of which it is possible to demonstrate the presence of tubercle bacilli in a comparatively short time. He inoculates guinea-pigs with material from patients. The injection is made into the animal's popliteal lymph nodes. Whenever the material contains tubercle bacilli, the lymph nodes become enlarged and hardened in the course of the second week following the inoculation. Then they are extirpated and crush preparations are made. These are stained and examined under the microscope. The entire process requires only about two weeks. The author performed this test on 150 animals.

MOSQUITOES: An Improved Deterrent, Dover, C. Indian J. Med. Res. 17: 961, 1930.

Citronella oil (Burgoyne's)	½ ounce
Spirits of camphor	¼ ounce
Cedar-wood oil	¼ ounce
White petroleum jelly (B.P.)	2 ounces

The petroleum jelly should be melted and the other constituents then added, the mixture being well stirred. Bottle (a 3-ounce wide-mouthed jar is a convenient size) and cool rapidly, preferably by placing the bottle (which should be kept closed) in a basin of cold water or in a refrigerator.

The formula forms a firm, whitish, nonstaining cream of pleasant odor which, in addition to its properties as a mosquito-deterrent, is soothing, antiseptic and beneficial to the skin (petroleum jelly, it will be remembered, is the base of most face creams). One application usually lasts for a whole night, and only a small quantity need be used on each occasion. To avoid using it on the face in the evenings, the cream has been employed by some as a brilliantine for the hair, as it was found that for a time this keeps mosquitoes away almost as successfully as if the whole face were smeared with it.

SPINAL FLUID: The Fiamberti and Rizzatti Test, Brogg, E. Rassegna di studi psichiat. **18**: 315, 1929.

At the eighth meeting of the Italian neurologic society at Naples, Fiamberti and Rizzatti proposed a new cerebrospinal fluid test as follows: One c.c. of a 1 per cent solution of hydrate of sodium, and 0.75 c.c. of a 1 per thousand potassium permanganate solution are placed in a small test tube. After shaking, 0.1 c.c. of cerebrospinal fluid to be examined is added and shaken again. If positive the mixture becomes bright green after thirty-minutes. If negative the color remains unchanged, or may tend to violet or blue without becoming green.

TUMORS: The Issues at Stake in the Grading of, Reimann, S. P. Arch. Path. **8**: 813, 1929.

An attempt to grade the relative malignancy of 100 cases of cancer of the breast from the histologic picture of specimens obtained at operation gave false results, as determined by the later history of the patients from the follow-up records. A discussion of the biologic basis of this outcome, together with an inquiry into the rationale of the histologic grading of tumors, has been made. The conclusion is that the grading of a tumor for the individual patient is impossible at present.

TISSUE: New Differential Stain for Connective Tissue Combined With Hematoxylin and Eosin, Larson, E. E. Stain Tech. **5**: 73, 1930.

The method works equally well for paraffin or celloidin sections and after any of the more common fixing solutions:

1. Stain in hematein solution two to three minutes (Hematein, Coleman and Bell, 1 gram dissolved in 10 c.c. of absolute alcohol and added drop by drop to 100 c.c. saturated aqueous ammonia alum).

Filter and add 25 c.c. glycerin and 25 c.c. methyl alcohol.

2. Tap water.

3. Eosin one minute or slightly longer (Eosin B, Coleman and Bell, 0.5 gm. to 100 c.c. 25 per cent alcohol).

4. Through alcohols to 95 per cent.

5. Orange G, fifteen seconds or less (Orange G, Coleman and Bell, 0.5 gm. to 100 c.c. 95 per cent alcohol).

6. Dehydrate in absolute alcohol, clear and mount.

The best demonstrations of the method were obtained on skin and stomach sections. In skin sections one can easily recognize the connective tissue fibers because they are stained a distinct yellow against the pink background. Not only are the bundles of white inelastic connective tissue fibers stained vividly by the orange G, but also the individual threads of the yellow elastic fibers. The contrast of blue epithelium, pink cytoplasm, and yellow connective tissue fibers is very striking. In the stomach sections the connective tissue of the submucosa is distinctly marked off because of its yellow color. The connective tissue fibers between the muscle fibers are also easily seen. In such an organ as the testes where there is so little connective tissue between the tubules, this method is even more satisfactory because it brings out the little connective tissue there is in contrast to the other tissue elements.

REVIEWS

Books for Review should be sent to Dr. Warren T. Vaughan, Medical Arts Building, Richmond, Va.

*Handbook of the Vaccine Treatment of Chronic Rheumatic Disease**

WITH the prevailing scepticism concerning the value of vaccines in arthritis among many, and with the lack of unanimity as to what vaccine is most appropriate among the rest, it is highly stimulating to find a booklet in which the writer feels so extremely confident that his own method will produce unusually good results.

The above is not written in irony but in all seriousness, for Dr. Crowe has demonstrated through twenty years of research his sincerity and ability. He is as confident as may be that a vaccine prepared from the organisms which he has succeeded in isolating will produce relief in the majority of cases of chronic infectious arthritis (atrophic and hypertrophic). This confidence is born of his own clinical experience.

Briefly, Crowe's experience has shown him that a large number of streptococci (at least 155), closely related but not immunologically identical, and two staphylococci, Micrococcus deformans, are involved in arthritis (both types). His results with stock vaccine containing these organisms are about as good as those with autogenous. He often combines both types of vaccine. He emphasizes the need for a small dosage. The patient should feel better rather than worse after a treatment.

The handbook under review presents details of treatment for those who may wish to investigate the value of Crowe's vaccine treatment. It is sequential and concise. This book, together with the author's other two volumes, previously reviewed in these columns, should be read by those who are seriously interested in the problem of arthritis.

Arthritis and Rheumatoid Conditions: Their Nature and Treatment†

AMONG the volumes on arthritis of recent years, we find three general classes: monographic, reviewing the writer's experimental contributions to the subject; essentially clinical contributions such as those written by physicians at spas and other health resorts; and comprehensive general reviews by recognized authorities into which have been incorporated and correlated the writer's own contributions to the subject.

Pemberton's volume may be described as the outstanding recent contribution in the third of these categories. In it we find all that is really of value on the subject: economic aspects, rôle of infection, pathology, and symptoms.

The section on pathology is especially to be recommended. It is well and abundantly illustrated and will enable those who may be confused by the multitude of classifications to understand clearly the differentiations. There are two sections in the division on pathology, the first on structural changes and the second on dynamic pathology. It is to this latter subject that the author's most valuable contributions have been made; for these alone the volume would be worth while.

Over half of the volume is devoted to a discussion of treatment. All phases thereof come in for discussion but the lesson to be gained from study of this section is that no single track line of therapy will be as successful as that in which the individual is considered as a physiologic unit and in which the patient as an individual as well as the local changes or symptoms is treated.

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*Handbook of the Vaccine Treatment of Chronic Rheumatic Diseases. By H. Warren Crowe, D.M., B.Ch., M.R.C.S., L.R.C.P., Director of the Charterhouse Rheumatism Clinic, Late Consulting Physician (vaccine treatment), Yorkshire Home for Incurable and Chronic Diseases. Paper, 52 pages. New York, 1930, Humphrey Milford Oxford, University Press, American Branch.

†Arthritis and Rheumatoid Conditions: Their Nature and Treatment. By Ralph Pemberton, M.S., M.D., Physician to the Presbyterian Hospital, Philadelphia; Associate Professor of Medicine, University of Pennsylvania Graduate School; Chairman, American Committee for the Control of Rheumatism, etc. Illustrated with 42 engravings and 1 colored plate. Cloth, 354 pages. Philadelphia, 1930, Lea and Febiger.

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EDITORIALS

A Symposium on Arthritis

IN THE cycle of medical interest certain diseases or disease groups come rather periodically to the fore. This is equally true with popular interest in medical subjects. Following the "Swat the Fly" campaign, the "Don't Spit" campaign, and the "Sanitary Drinking Cup" campaign, all of which developed along with the growth and activities of the National Tuberculosis Association, interest next centered in eugenics, with consequent development of eugenic societies and race betterment associations. Then came the popular interest in cancer.

In both medical and popular circles, flare-ups of interest in certain subjects depend, naturally, on various causes. A new discovery holds out hope of an early Utopia; an apostle sways the multitude in the direction of his own interest and enthusiasm; a disease such as influenza, almost forgotten, claims our interest because of its returning prevalence.

Rather in contrast to this, there are problems in medicine which are with us at all times—problems toward the solution of which many of our most

capable workers are bending their best endeavors, concerning which it seems well to direct general attention from time to time in order that we may become cognizant of what progress is being made and of how diverse or even conflicting observations are being, or must be, correlated or reconciled.

The symposium idea in publications, while in no way new in this country, has been applied rather more successfully among certain of the more prominent continental journals.

A symposium, to be of the greatest value, should not be a series of discussions or a sequence of etiology, pathology, symptomatology, diagnosis, and therapy, contributed by reviewers whose qualifications rarely justify their being termed authorities. Rather should it be a series of presentations by leading authorities in their fields. Nor need the individual contributions be closely correlated. The reader will have no difficulty in providing his own correlations. Too often attempts to fit one's contribution into the pattern of a mosaic lessens the forcefulness of the contribution as an independent unit.

Some clinical journals have rather specialized on symposia, but as a rule they have been of a group which lacked sufficient prestige to interest the leaders in the fields in contributing. There can be no doubt that the symposium idea is an excellent one provided the contributions are from men of eminence. Symposia at medical conferences, the Symposium on Nephritis just terminated at the University of Minnesota, volumes such as those recently edited by Jordan and Falk, by McClung, by Rivers, and by Cowdry bear evidence of this.

It is for reasons such as these that the editor is glad to offer to the readers of the JOURNAL a symposium which is of general interest, both in its clinical and its laboratory aspects. If the subscribers should judge it a success and should desire additional symposia on topics of interest we will be glad to issue others occasionally. The new and original contributions herein were made on invitation and the editors express their deep appreciation to the essayists for their interest and cooperation.

One who reads the pages of this number* will recognize at once the tremendous economic importance of the subject under discussion and its diverse aspects. To those who have made no intensive study of the subject, the many facets of the investigations will be stimulating. The variety of etiologic factors, infection (several different organisms are suggested), colonic absorption, local nutritional disturbances, endocrine imbalance, dietary factors, climate, even the possibility of protozoan infestation, all come in for discussion.

Dr. Ely has said, "One of the most popular methods of treating patients with arthritis is to send them to some one else." This, regrettably, is too often true, and if continued from physician to physician in an endless chain, deprives the victim of the disease of those perfectly definite and helpful therapeutic aids which have so far been established and are his by right.

It is in the hope that these essays will stimulate the clinician to a broader and more intensive therapeutic outlook and a greater interest in the welfare of his arthritic patient, and the pathologist to renewed efforts to solve the mysteries of the disease that this symposium is offered to our readers.

—*W. T. V.*

*It was originally planned to have but one number devoted to a symposium on arthritis, but on account of the length and excellence of the material we have decided to issue it in two numbers.

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News Item

The following officers were elected at the June meeting:

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